from HMW polymers. In the supplemental literature search, 1218 articles were identified on PubMed and Embase (combined). Title and abstract screening resulted in46 potentially relevant articles for full text screening. Of these, 13 were identified as potentially relevant for review. Complete details on the systematic review are provided in the Supporting Information file at "Section 1 Systematic Literature Review".

Commented [HT25]: How many overlap with the 51 from first search/review?

Commented [ST26R25]: I will add this, need to double check

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries develop the health effects summaries in the section on Hazard Identification and identify NAMs to include in the section on Tiered-Testing Strategies.

Category Boundaries

The category boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA's polymer exclusion criteria, is discussed further below. It should be noted that even if a HMW polymer satisfies the category boundary criteria, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

Commented [ST27]: Modified text

Commented [JA28R27]: Nice addition

In humans, ~~R~~respirable particles are those chemical substances with an aerodynamic particle size of less than or equal to 10 µm. The cutoff of 10 µm, as defined by EPA in its "Air Quality Criteria for Particulate Matter", represents "particles collected by a sampler with an upper 50% cut point of 10 µm D_a [aerodynamic diameter] and a specific, fairly sharp, penetration curve" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/

600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. However, depending on the sampling method and size fraction collected, the sample may contain particles between 10 and 30 μm diameter that are excluded from the 10 μm D_a fraction [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>].

In comparison, occupational health organizations rely on unified size fraction definitions based on the upper size cuts of particles and entry into the different regions of the respiratory tract. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) considers 10 μm D_a particles as an upper limit for particles with this size entering the alveolar region [

ADDIN EN.CITE <EndNote><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><DisplayText>[24]</DisplayText><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Further, consideration must also be given to particle settling that may occur. For example, in still air, 10 μm spherical particles with a density of 1 g/cm^3 can remain airborne for approximately 8 minutes [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne

Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. However, as particle size decreases, the airborne settling time increases (*e.g.*, approximately 1.5 hours for 3 µm particles to settle in still air) [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[24, 25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><record><rec-number>52</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Therefore, solids with even a small fraction of respirable particles may produce prolonged and elevated airborne levels of respirable particles in the workplace. Though occupational monitoring data provide the most direct assurance that airborne levels of respirable particles do not exceed relevant exposure limits, particle size distribution data are typically the only metric available for estimating potential respirability for new chemical substances. Given this limitation and the reality that nearly all solid particulate materials may contain some percentage of respirable particles, a practical screening cutoff is warranted for category inclusion/exclusion.

For the purposes of defining this category, we propose that HMW polymers are considered respirable if they are manufactured, processed, used, *etc.*, in a manner that generates the new chemical substance with a particle or aerosol size of less than or equal to 10 μm or if respirable particles may be unintentionally generated during the life cycle of the material (*e.g.*, impaction and friction during transport). Under the latter scenarios, a practical cutoff of $\geq$ 1% respirable particles by weight (wt%) as the cutoff for assessing respirable particles and this percentage would be based on particle size distribution data for the material. The practical cutoff of $\geq$ 1 wt% is the same cutoff EPA applies to the nonreportable content of nanoscale materials [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>54</RecNum><DisplayText>[26]</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791830">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. This same cutoff would apply to the particle/droplet size distribution in the case of aerosols of a solid or liquid chemical substance and would be determined based on droplet size data for the material and/or liquid application method (*e.g.*, spray, aerosol, mist).

EPA's FG and FGEW criteria for E1 polymers provide a starting point for evaluating the potential reactivity and/or cytotoxicity of HMW polymers. Therefore, we propose using these criteria as an initial screen for determining whether a HMW polymer is considered non-reactive or reactive and included or excluded from the category, respectively. As shown in [REF

_Ref46665925 \h * MERGEFORMAT], the E1 polymer exemption criteria include low-concern, moderate-concern, or high-concern FGs. A summary of representative FGs meeting each of these hazard concern levels is shown in [REF _Ref46674358 \h * MERGEFORMAT].

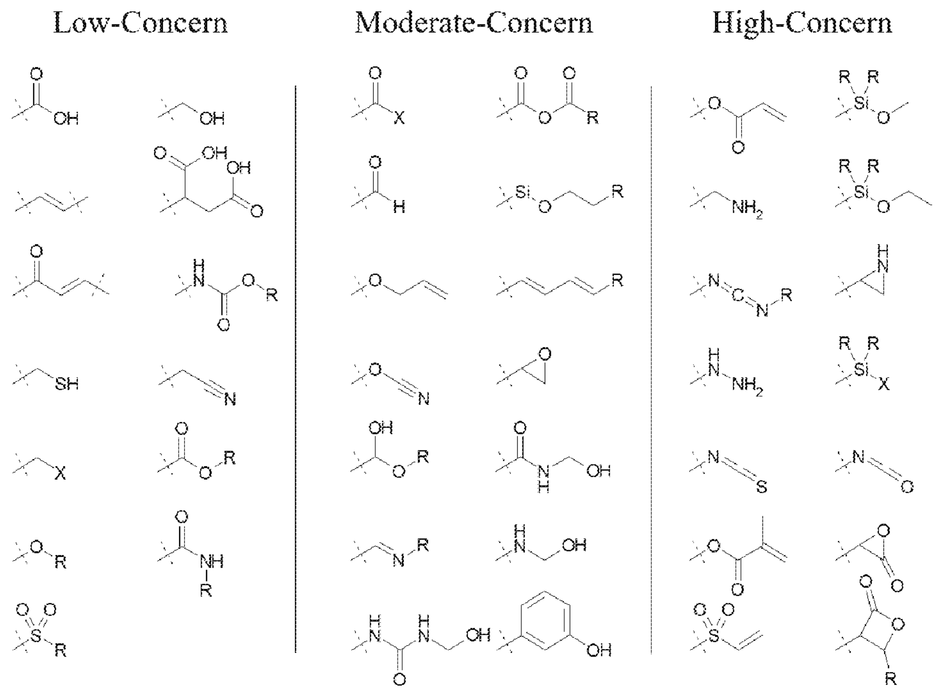


Figure [SEQ Figure * ARABIC]. FG hazard concern levels for polymeric substances meeting EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern) for the HMW polymer category. The following cutoffs are proposed as the category boundaries for establishing that a HMW polymer is non-reactive: low-concern FGs (no limit), moderate-concern FGs (FGEW $\geq$ 1,000), or high-concern FGs (FGEW $\geq$ 5,000). "R" represents an undefined structure; “X” represents a halide. See: EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] for further details.

A generally recognized property of respirable, low reactive (*i.e.*, low toxicity) particles that can cause lung overload is the poorly soluble nature of these compounds. EPA has published general water solubility classifications, which include: negligible solubility (*i.e.*, < 0.1 mg/L), slight solubility (*i.e.*, > 0.1 - 100 mg/L), moderate solubility (*i.e.*, > 100 - 1,000 mg/L), soluble (> 1,000 - 10,000 mg/L), and very soluble (> 10,000 mg/L) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>56</RecNum><DisplayText>[27]</DisplayText><record><rec-number>56</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595792442">56</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Section 5. Estimating Physical/Chemical and Environmental Fate Properties with EPI SuiteTM, Sustainable Futures/P2 Framework Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>22, https://www.epa.gov/sites/production/files/2015-05/documents/05.pdf</pages><volume>EPA-748-B12-001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].
These values were not established for evaluating the solubility of particles for lung overload; however, they may be used as conservative cutoffs for extractability, per OECD TG 120 [
ADDIN EN.CITE
<EndNote><Cite><Author>OECD</Author><Year>2000</Year><RecNum>55</RecNum><DisplayText>[28]</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792078">55</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Solution/Extraction Behaviour of Polymers in Water</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>4, https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-

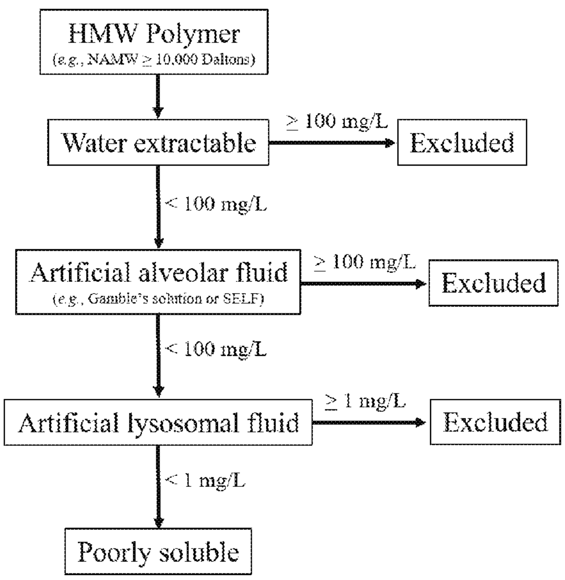
chemical-properties_20745753</pages><volume>120</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>], for measuring the insolubility/solubility of HMW polymers. ECETOC (2013) [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>] proposed an initial biosolubility screening approach that provided qualitative determinants (*i.e.*, “soluble”, “insoluble”, “Low dissolution rate”, or “Very high dissolution rate”) for assessing biosolubility; however, no quantitative thresholds were provided. In comparison, the International Commission on Radiological Protection (ICRP) and the German Federal Institute for Occupational Safety and Health (FIOSH) provide quantitative biosolubility cutoffs. ICRP describes three categories of soluble radiological materials: Fast (all material rapidly dissolves at a rate of 100 day^{-1}), Moderate (10% of the material dissolves rapidly and the rest dissolves at a rate of 0.005 day^{-1}), and Slow (0.1% of the material dissolves rapidly and the rest dissolves at a rate of 0.0001 day^{-1}) [

ADDIN EN.CITE
<EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</

year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. FIOSH proposed a simulated solubility threshold of ≤ 1 mg/L in artificial lung fluids for identifying particles as "low soluble dusts" [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[30]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

As discussed ~~previously~~ above, the screening particle size cutoff and percentage of respirable particles for inclusion in this HMW polymer category are ≤ 10 µm and ≥ 1 wt%, respectively. These criteria are readily determinable based on the intended use and life cycle of the HMW polymer. However, determining whether a HMW polymer is "poorly soluble" and a potential hazard concern for lung overload is also dependent on the potential daily exposure estimates. Therefore, we propose using the inclusion/exclusion cutoffs shown in [REF _Ref46673847 \h * MERGEFORMAT], which consider water extractability or /biosolubility and the legally binding permissible exposure limit (PEL), as mandated by the U.S. Occupational Safety and Health Administration (OSHA) for respirable particulates not otherwise regulated or PNOR (*i.e.*, 5 mg/m^3).

Scheme [SEQ Scheme * ARABIC]. Screening criteria for determining water extractability and biosolubility.



The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first screen is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility classifications were not specifically established to identify potential hazards related to lung overload and have not been established to correlate with either biosolubility or biopersistence. Therefore, EPA's cutoff for moderate water solubility (*i.e.*, 100 mg/L) was selected rather than the low water solubility cutoff, since it represents a transition from slight to moderate water solubility and is therefore expected to be conservatively inclusive in the first step because water extractability is generally expected to overestimate the insolubility of polymers in biological fluids.

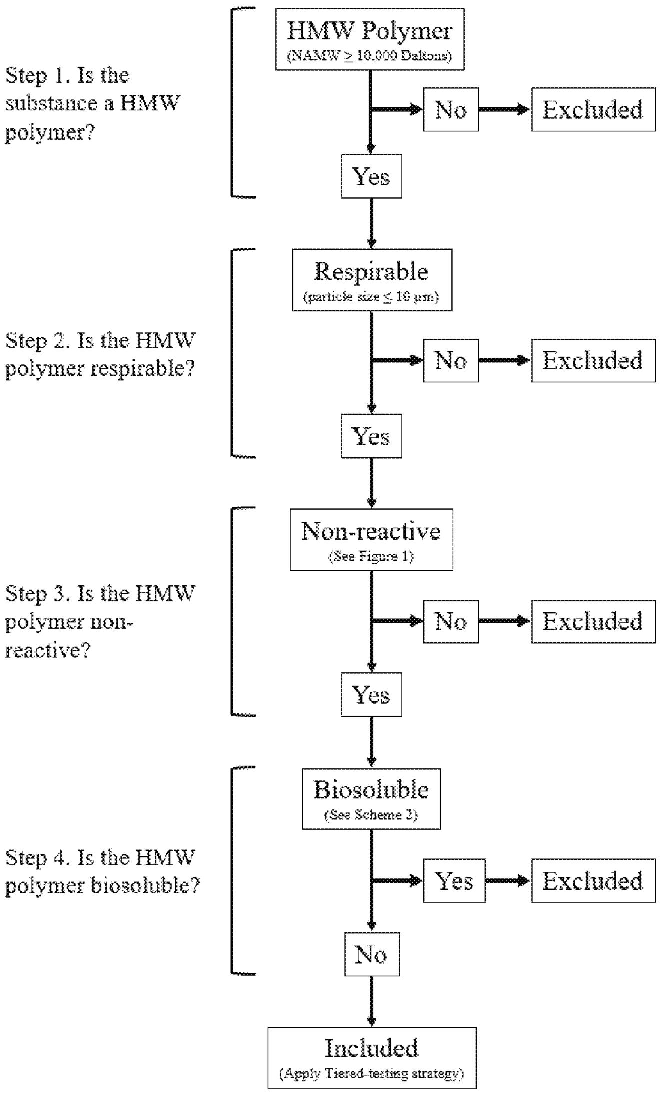
In the second screen, two biosolubility cutoffs may be used, either 100 mg/L or 1 mg/L, depending on the test system used (*e.g.*, simulated epithelial lung fluid or artificial alveolar macrophage lysosomal fluid). These values account for the biosolubility of the HMW polymer, as well as the Permissible Exposure Level (PEL) for ~~OSHA~~ Particulates Not Otherwise Regulated (PNOR) ~~PEL~~ of 5 mg/m^3 (*i.e.*, 50 mg/day; 5 mg/m^3 × 10 m^3/day) for the respirable fraction from the Occupational Safety and Health Administration (OSHA). The first value is based on EPA (2020) [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>75</RecNum><DisplayText>[31]</DisplayText><record><rec-number>75</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595843741">75</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Revocation of Significant New Use Rule for a Certain Chemical Substance (P-16-581), Proposed rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-

Commented [JA29]: CHECK on definition title>Federal Register</full-title></periodical><pages>18179-18181</pages><volume>85</volume><number>63</number><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], where the Agency applied a biosolubility cutoff of approximately 100 mg/L/day for a polymer in simulated epithelial lung fluid. This value would equate to a mean dissolution rate of approximately 72 mg/day in humans, based on an estimated daily alveolar fluid turnover of 0.72 L [ADDIN EN.CITE <EndNote><Cite><Author>Fronius</Author><Year>2012</Year><RecNum>58</RecNum><DisplayText>[32]</DisplayText><record><rec-number>58</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595795295">58</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fronius, M.</author><author>Clauss, W.G.</author><author>Althaus, M.</author></authors></contributors><titles><title>Why do we have to move fluid to be able to breath?</title><secondary-title>Frontiers in Physiology</secondary-title></titles><periodical><full-title>Frontiers in Physiology</full-title></periodical><pages>5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357553/pdf/fphys-03-00146.pdf</pages><volume>3</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The second value is based on the German Federal Institute for Occupational Safety and Health (FIOSH) biosolubility cutoff of 1 mg/L for granular biopersistent particles. We propose application of this cutoff as a surrogate for estimating the biosolubility HMW polymers in the lysosomes of alveolar macrophages (*e.g.*, artificial lysosomal fluid).

The above screening criteria for respirability, reactivity, and biosolubility provide a framework for determining inclusion/exclusion from the HMW polymer category, as shown in Scheme 2. The screening criteria may be used for determining whether further evaluation of the new chemical substance is warranted using the tiered-testing strategy discussed later in this document.

Scheme [SEQ Scheme * ARABIC]. Framework for determining whether a chemical substance is included/excluded from the HMW polymer category.



Based on the above information, the HMW polymer category was defined to include a variety of respirable, non-reactive (*i.e.*, low toxicity), and poorly soluble HMW (*i.e.*, ≥ 10,000 Daltons) materials, which meet the above-stated criteria for these parameters. HMW polymers meeting these criteria are those which are typically formed through various polymerization processes. Chemical substances included are branched and linear polymers, as well as co-polymers produced by random, block, graft, or other techniques. Crosslinked polymers were included in the category because crosslinking can decrease water solubility, but crosslinking was not necessary for inclusion. Therefore, the representative members of this category were refined to include polyacrylates/methacrylates, polyvinyl polymers, polyamides, and polyurethanes/polyureas. The water-dispersible forms polyacrylates/metacrylates and polyurethanes/polyureas would not present hazards for lung overload and are not included in the HMW polymer category [ADDIN EN.CITE ADDIN EN.CITE.DATA]; however, despite their exclusion from the category, they would need to be assessed for other potential hazard concerns. A summary of the structural features of these chemical substances and the chemical boundaries that were established is shown in [REF _Ref46674591 \h * MERGEFORMAT].

[EMBED ChemDraw.Document.6.0]

Figure [SEQ Figure * ARABIC]. Representative members of the HMW polymer category. Structure A is representative of polyacrylate/methacylate members, where R is H or methyl; R' and R'' are typically alkyl or substituted alkyl, although there are currently no limits on the substituents. However, charged groups such as carboxyl groups or amine groups would tend to make the polymer dispersible in water rather than insoluble in water. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Acrylamide and methacrylamide monomers (NR'_2 replaces OR' or OR") may also be present. Structure B is representative of polyvinyl members, where R is H or C1-C > 20. R' is typically methyl, CN, acetyloxy, Ph or Cl, although there are no current limits on R'. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Copolymers (e.g., including both acrylate/methacrylate and vinyl monomers) are also members of this category. Structure C is representative of the polyamides group and is made of condensation polymers in which the linkages are all amide functional groups. An example is polycaprolactam, shown.

Hazard Identification

TSCA and its implementing regulations do not require upfront testing on new chemical substances. Therefore, when assessing new chemical substances, EPA generally identifies toxicological analogues to inform the potential hazards for the new chemical substances. The

systematic review of the literature was used to identify inhalation studies that assessed endpoints indicative of “overload” for potential toxicological analogues. For the purpose of defining this chemical category, overload has the same definition as identified by EPA (1996) [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>59</RecNum><DisplayText>[35]</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797014">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume II of III</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>774, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=219821</pages><volume>EPA/600/P-95/001bF</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]: “This is defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of poorly soluble particles (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in A [alveolar] region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of

particles into the interstitium." The relevant studies that were identified are summarized below, followed by the selection of studies on toxicological analogues that may serve as representative points of departure for assessing the potential hazard for overload of some new chemical substances.

Human Data

The hazard concerns discussed herein are limited to chronic effects in the ~~lower respiratory tract~~ pulmonary (alveolar) region of rats exposed to HMW polymers. Epidemiological studies have shown increased lung burdens in workers chronically exposed to poorly soluble particles (PSPs), such as former coal miners; however, studies have shown that rodent models overpredict lung burdens in humans if adjustments are not made for kinetic differences in clearance and retention [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This is consistent with findings from well-conducted epidemiological studies, which have not identified an association between occupational exposure to PSPs and an increased cancer risk. Oberdorster (1995) [ADDIN EN.CITE

<EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[36]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-

title></periodical><pages>123-135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>] concluded that “evidence in humans suggest that particle-overloaded lungs, *e.g.*, in coal workers, respond with fibrosis, but no increased incidence in lung tumors has been found in this group”. It has also been reported that “epidemiological data from production workers demonstrate no correlation between PSP exposure and lung cancer or other non-malignant respiratory diseases” [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Though these investigations focused on PSPs, the available, yet limited data on HMW polymers provide comparable results. For example, in a recent retrospective study of Xerox workers employed between 1960 and 1982, workers exposed to toner did not show an increased risk of “all-cause” or “cause-specific” mortality. The categories evaluated included cancer (*e.g.*, lung), diabetes, cardiovascular disease, and others [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Aside from this one epidemiological study on toner exposures, the available studies that evaluated potential hazards from exposures to HMW polymers were limited to inhalation studies conducted in experimental animals as summarized below and described in further detail in Section 2 “Experimental Animal Inhalation Studies on HMW Polymers” of the Supplemental Information file.

Animal Data - Noncancer Effects

Inhalation studies performed in rats and hamsters have demonstrated effects ranging from inflammation to fibrosis after inhalation exposure to several HMW polymers including print toners comprised largely of styrene/butylmethacrylate copolymer and polyvinyl chloride dust. Several of these studies were conducted according to validated test guidelines and under good laboratory practice (GLP) standards, and in some cases published in the peer-reviewed literature. A summary of these studies is provided below.

A series of sub-chronic and chronic studies were performed to test the inhalation effects of a water-insoluble styrene/butylmethacrylate polymer (the primary component of toner used in copy machines) of MW 70,000 in rats. In a subchronic 13-week study, rats were exposed to aerosol concentrations of toner at 0, 1, 4, 16, and 64 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. Dose-related increased lung weight and histological lesions (thickening of alveolar structure due to hypertrophy and hyperplasia of Type II cells) were seen in animals exposed to 16 and 64 mg/m^3. These exposure concentrations also resulted in a dose-related decrease in lung clearance, as measured by the retained quantity of the test substance in excised lungs, and increased lung particle burden [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-
360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><
urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-
resource-num></record></Cite></EndNote>]. The NOAEC from this study was 4 mg/m^3.

Bellmann *et al*. (1992) [ADDIN EN.CITE
<EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><
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type><contributors><authors><author>Bellmann, B.</author><author>Muhle,
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91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Anim
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rd><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug

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0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>] performed an additional 13-week study using the same test substance used by Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>] and included an extended 15-month post-exposure monitoring period. Rats were exposed to aerosol concentrations of toner at 0, 10, or 40 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study authors measured retention of the toner in the lungs and lung-associated lymph nodes (LALN) by photometric determination in dissolved tissues; clearance was monitored using tracer particles, and pulmonary effects were identified from enzymatic activities and differential cell counts in bronchoalveolar lavage fluid (BALF). The study authors identified clearance half-lives of 277 and 2,845 days for the low- and high-dose exposure groups, respectively, and reported pulmonary effects, as evidenced by increases in protein and enzyme markers of tissue damage in BALF that were partially reversible at 10 mg/m^3 and not reversible at 40 mg/m^3 [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health

Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
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Muhle *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>] and Bellmann *et al*. (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1991</Year><RecNum>3</RecNum><

DisplayText>[42]</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844572">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Kilpper, R.</author><author>MacKenzie, J. C.</author><author>Morrow, P.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats</title><secondary-title>Fundam Appl Toxicol</secondary-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>300-13</pages><volume>17</volume><number>2</number><edition>1991/08/01</edition><keywords><keyword>Aerosols</keyword><keyword>Animals</keyword><keyword>Body Burden</keyword><keyword>Dust/adverse effects</keyword><keyword>Female</keyword><keyword>Half-Life</keyword><keyword>Lung/*metabolism</keyword><keyword>Lymph Nodes/metabolism</keyword><keyword>Male</keyword><keyword>Pulmonary Alveoli/metabolism</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Sex Factors</keyword><keyword>Silicon Dioxide/*metabolism</keyword><keyword>Titanium/*metabolism</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590 (Linking)</isbn><accession-num>1662649</accession-

num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1662649</url></related-urls></urls><electronic-resource-num>10.1016/0272-0590(91)90220-x</electronic-resource-num></record></Cite></EndNote>] reported findings from a chronic 24-month exposure study in rats exposed to toner at aerosol concentrations of 0, 1, 4, or 16 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study was performed according to OECD No. 453 Combined Chronic Toxicity/Carcinogenicity Studies and under GLP standards. The study authors reported dose-related impaired particle clearance, elevated lung particle burden, and lung effects (fibrosis, BALF markers of tissue damage, and increased lung weight) at 4 and 16 mg/m^3, with a NOAEC of 1 mg/m^3.

Unpublished subchronic (3 months) and chronic (18 months) hamster studies of the same print toner tested by Muhle *et al*. (1990, 1991) and Bellman *et al*. (1991, 1992) [ADDIN EN.CITE ADDIN EN.CITE.DATA] showed effects similar to those in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The unpublished 3-month study was hampered by disease and mortality unrelated to treatment. In the unpublished 18-month study, the hamsters were exposed to concentrations of 0, 1.5, 6, or 24 mg/m^3 for the first 5 months and then concentrations of 0, 4, 16, or 64 mg/m^3 for the remaining time. At all exposure concentrations, the hamsters exhibited macrophage accumulation, interstitial inflammatory cell infiltration, and bronchiolar/alveolar hyperplasia, along with particle deposits and lymphatic hyperplasia in the LALNs. At the mid- and high-exposure concentrations, fibrosis and alveolar PMN infiltration were noted at the end of exposure and/or after the 5 month post-exposure recovery period; the highest exposure group also exhibited increased lung weight and effects on BALF parameters (increased cell number, macrophage count, LDH, β glucuronidase, total protein, and hydroxyproline). The LOAEC for this study was in the range of 1.5 to 4 mg/m^3.

Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] performed an eight-month inhalation study in rats exposed to an aerosol of PVC powder at 0, 3.3, 8.3, or 20.2 mg/m^3 (MMAD = 1.3 μm; GSD = 2.07; density = 1.3 g/cm^3) for 5 hours/day, 5 days/week. Retention, clearance, and pulmonary effects were evaluated, as reported previously by these same authors. Using radiolabeled (^{85}Sr) polystyrene particles as tracers, these authors showed that pulmonary clearance was significantly decreased in rats after seven months of exposure (25 hours per week) to PVC powder at concentrations ≥ 3.3 mg/m^3. Mean alveolar clearance half-times increased with exposure from 1.2-fold higher than controls to 3.2-fold higher than controls at concentrations from 3.3 to 20.2 mg/m^3. The study authors calculated half-times for alveolar clearances of 71, 122, and 184 days at exposure concentrations of 3.3, 8.3, and 20.2 mg/m^3, supporting that lung overload occurred at concentrations ≥ 3.3 mg/m^3 for this water-insoluble polymer.

Animal Data - Cancer

Chronic inhalation exposure data specifically pertaining to HMW polymers are limited to a 24-month rat study of print toner and an 18-month hamster study of print toner [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-

title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>]. No increased tumor incidence was observed in either study; however, interstitial and alveolar lung pathology has been documented in long-term inhalation studies on these polymers. See section on "Animal Data - Noncancer Effects" above.

Supporting Information

An *in vitro* study was identified and reviewed that may be relevant for determining the reactivity/non-reactivity of HMW polymers that do not meet the initial FG and/or FGEW screening criteria.

Wiemann et al. (2016) [ADDIN EN.CITE ADDIN EN.CITE.DATA] developed an *in vitro* assay to test nanoparticles for biologically active toxicity from passive (*i.e.*, overload condition) toxicity. The assay uses rat NR8383 alveolar macrophages incubated with test material in cell culture medium, and assesses toxicity *via* measurement of LDH, glucuronidase, and tumor necrosis factor α (TNFα) (after 16 hours exposure), and hydrogen peroxide (after 1.5 hours) in the cell culture supernatant. The authors tested 18 inorganic nanomaterials using the assay, as well as corundum as a negative control and quartz DQ12 as a positive control. Based on data from short term inhalation studies, each test material was categorized as either active (NOAEC <10 mg/m^3 for adverse inflammatory action in a 5-day inhalation study) or passive (*i.e.*, inducing nonspecific cell overload). The *in vitro* assay threshold for active toxicity was a surface-area/volume concentration of 6,000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL) in at least two of the four parameters measured in supernatant. The nanomaterials tested showed good correspondence between the *in vitro* and *in vivo* parameters (assay accuracy 95%), suggesting that, the assay could be useful in distinguishing specific ("active") toxicity from nonspecific ("passive" or overload) effects on alveolar macrophages. Although only nanoparticles were tested by these authors, this assay may be useful for screening out HMW polymers for inclusion/exclusion in the category, *e.g.*, those identified as "active" would be inconsistent with the low-concern level and inclusion in the category, whereas those identified as "passive" appear to be consistent with inclusion. Additionally, this assay could be useful for screening polymers with specific toxicities (*i.e.*, excluded from overload category) prior to *in vivo* testing of "overload" for passive polymers.

Commented [JA30]: Need to provide size range

Commented [JA31]: WHAT was the dose metric for comparison??

Quantitative Points of Departure (PODs)

A single epidemiological study of inhaled HMW polymers was identified - the retrospective study of Xerox workers [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This study did not report exposure concentrations associated with the evaluated health outcomes and is therefore not useful for determining quantitative PODs for pulmonary effects of HMW polymers.

A summary of animal studies documenting pulmonary effects after exposure to HMW polymers and the PODs identified from them is provided in [REF _Ref46678612 \h * MERGEFORMAT]. The PODs presented in the table include those from studies meeting the following criteria:

- Exposure was *in vivo via* inhalation (*in vitro*, intratracheal instillation studies were not included);
- Exposure continued for at least 13 weeks; and
- Critical study information was reported, including exposure concentrations, exposure regimen, and aerodynamic particle size distribution (MMAD and GSD).

Commented [JA32]: What about DENSITY??

Each study was evaluated to determine whether the data were amenable for BMD modeling.

For the polyacrylates and methacrylates subcategory, several subchronic studies are included in [REF _Ref46678612 \h * MERGEFORMAT] that met the initial POD selection criteria; however, BMD modeling was not performed on these studies because chronic studies were available and deemed more relevant for the hazard assessment.

Commented [JA33]: ?? BOTH subchronic and chronic are relevant

Two chronic studies met the POD selection criteria: the published 24-month rat study of 9000 type toner and the unpublished 18-month hamster study of the same toner [ADDIN EN.CITE ADDIN EN.CITE.DATA]. BMD modeling was performed for the data in the rat study performed by Muhle *et al*. (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-

resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>], as it used a longer exposure duration, was published in a peer-reviewed journal, and did not change exposure concentrations during the study, whereas, in the hamster study, exposure concentrations were modified after the first five months. Among the endpoints affected at the LOAEC in that study (macrophages, PMN, and lymphocytes in BAL; incidence of pulmonary fibrosis), only the fibrosis incidence could be modeled, as the BALF parameters were reported without measures of variability (*i.e.*, standard deviation or standard error). The incidences of lung fibrosis (summed across severity categories) were subjected to BMD modeling, as described in Section 3 "Benchmark Dose (BMD) Modeling Outputs" of the Supplemental Information file. The BMCL from the best-fitting model was 2.5 mg/m^3, as shown in [REF _Ref46678612 \h * MERGEFORMAT].

Only a single study was available for the polyvinyl subcategory; however, BMD modeling on the alveolar clearance for the tracer was not possible because of the absence of reported measures of variability ([REF _Ref46678612 \h * MERGEFORMAT]).

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyacrylates and Methacrylates Sub-category							
9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rats, male and female (288/group); 24 months (6 hr/d, 5 d/wk), 2 months recovery	0, 1, 4, or 16	1	4	2.5 (fibrosis)	Significantly decreased macrophages and increased PMN and lymphocytes in BAL; significantly increased incidence of minimal to mild pulmonary fibrosis	[ADDIN EN.CITE ADDIN EN.CITE.DATA]

9000 Toner (styrene/butylmethacrylate random copolymer)	Syrian Golden Han:AURA Hamster, male and female, (50/group); 18 months (6 hr/d, 5 d/wk); 3-5 mo. recovery	0, 1.5, 6, or 24 (months 1-5); 0, 4, 16, or 64 (months 6-18)	ND	1.5-4	Not derived; variable exposure regimen	Significantly increased incidences of bronchiolar/alveolar hyperplasia (males); accumulation particle-laden macrophages in lungs; interstitial inflammatory cell infiltration in lungs (males); lymphatic hyperplasia in LALN (males); and particle deposits in LALN	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>30</RecNum><DisplayText>[49]</DisplayText><record><rec-number>30</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849152">30</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho

							fer Institute</author></authors></contributors><titles><title>An investigation of the biological effects of a toner fraction. Final Report of a subchronic inhalation study in Syrian Golden hamsters. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0513473-2</title></titles><dates><year>1991</year></dates><publisher>Xerox Corporation</publisher

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							><urls></urls></record></Cite></EndNote>]

Toner A (styrene/butylmethacrylate random copolymer)	F344/CrlBR rat, female, (58-66/group); 3 months (6 hr/d, 5 d/wk); up to 6 mo. recovery	0, 4, 16, or 64	ND	4	Not derived	Significantly increased incidence slight to moderate accumulation of particle-laden macrophages in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>28</RecNum><DisplayText>[43]</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848985">28</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho

							fer Institute</author></authors></contributors><titles><title>An investigation of the biological effects of a toner fraction in a subchronic inhalation study in rats (Toner A). Final Report. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0513473-7</title></titles><dates><year>1991</year></dates><publisher>Xerox Corporation</publisher><urls></urls></record

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							></Cite></EndNote>]

9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rat, female (≥18/group); 3 months (6 hr/d, 5 d/wk), 15 months recovery	0, 10, or 40	ND	10	Not derived	Significantly decreased alveolar clearance	[ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellman

							n, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health Perspect</secondary-title></titles

							><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keywor

							d><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><d

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0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite>

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							</EndNote>]

9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rat, male and female (56-74/sex/group); 3 months (6 hr/d, 5 d/wk), 3 months recovery	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased relative lung weight in males; histopathology showed a few particles in alveolar walls and a slight degree of thickening of the alveolar structure due to hypertrophy and hyperplasia of Type II cells and accumulation of a few interstitial cells; slightly enlarged LALN; decreased alveolar clearance	[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle,

							H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author> Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title>

							<secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>]

Toner B (styrene/ butadiene random copolymer)	F344 rat, female (50 rats/group for main study) up to 6 mo. recovery	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased incidence very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>29</RecNum><DisplayText>[50]</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849070">29</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho

							fer Institute</author></authors></contributors><titles><title> An investigation of the biological effects of a toner fraction in a subchronic inhalation study in rats (Toner B). Final Report. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0513473-7</title></titles><dates><year>1991</year></dates><publisher>Xerox Corporation</publisher><urls></urls></record

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							></Cite></ EndNote>]
Polyvinyls Sub-Category							

Polyvinyl chloride Powder	Rat, female (strain not reported); group sizes not reported; 8 months (25 hr/wk); up to 100 d recovery	~~0, 3.3, 8.3 or~~ 20.2	ND	3.3	Not derived; missing SD/SE	~~Significantly decreased alveolar clearance~~ Dose dependent increase in PMN at 8 months	[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle,

Commented [JA34]: ?? They were F344 and that is what was used in MPPD; also effects on PMN!!

							H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodica

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							l><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]

Study Selection for establishing sub-category points of departure (PODs)

In rats, the key events in the development of lung tumors in rats in response to inhalation of inorganic PSPs of low toxicity (as outlined by ECETOC 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>], Bevan *et al*., 2018 [ADDIN EN.CITE ADDIN EN.CITE.DATA], Driscoll and Borm, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Driscoll</Author><Year>2020</Year><RecNum>40</RecNum><DisplayText>[52]</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595775199">40</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Driscoll, K. E.</author><author>Borm, P. J. A.</author></authors></contributors><auth-address>Healthcare Innovation Partners, Princeton, NJ, USA.
Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.
Nanoconsult BV, Meerssen, The Netherlands.
Dusseldorf University, Dusseldorf, Germany.</auth-address><titles><title>Expert workshop on the hazards and risks of poorly soluble low toxicity particles</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>53-62</pages><volume>32</volume><number>2</number><edition>2020/03/10</edition><keywords><keyword>*pslt</keyword><keyword>*hazard</keyword><keyword>*inhalation</keyword><keyword>*lung cancer</keyword><keyword>*lung particle overload</keyword><keyword>*particles</keyword><keyword>*risk</keyword></keywords><dates><year>2020</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0895-8378</isbn><accession-num>32149535</accession-num><urls></urls><electronic-resource-num>10.1080/08958378.2020.1735581</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]) are: (1) impaired pulmonary clearance, (2) persistent neutrophilic inflammation, (3) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and (4) proliferation of cells initiated by secondary genotoxicity (from ROS, RNS, and/or inflammation) and tumor formation.

Though the key events for lung overload from HMW polymers have not been thoroughly studied, the available data as reviewed herein suggests that HMW polymers may lead to lung overload in the rat through similar key events. It should be noted that cytotoxicity to macrophages by a poorly soluble HMW polymer or components present in the polymer may negatively impact clearance *via* alveolar macrophages, thereby leading to tumor formation in humans. However, substances with these properties (*i.e.*, cytotoxicity) would not be included within the boundaries for the HMW polymers category.

Of the studies listed in [REF _Ref46678612 \h * MERGEFORMAT], PODs of 2.5 mg/m^3 and 3.3 mg/m^3 were identified for the polyacrylates/ methacrylates sub-category and the polyvinyls sub-category, respectively. The 24-month study on the 9000 Toner with a BMCL$_{10}$ of 2.5 mg/m^3 for pulmonary fibrosis was selected as a principle study for polyacrylates/methacrylates because it was the longest duration study on this sub-category of materials and was conducted in the most susceptible species for lung overload (*i.e.*, the rat). Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] was selected as a principle study for identifying a LOAEC of 3.3 mg/m^3 for the polyvinyls sub-category because it was based on decreased alveolar clearance, which is the first key event in the proposed adverse outcome pathway for lung overload from PSPs in the rat [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These study PODs represent potential starting points for evaluating new chemical substances that fit within one of the HMW polymer sub-categories. EPA may determine that either of these PODs is an acceptable toxicological analogue for chemistries that do not fit within the sub-categories but are anticipated to have comparable or greater potential for causing lung overload in the rat than the new chemical substance under evaluation. For example, EPA generally uses the POD of 3.3 mg/m^3 for quantifying the potential risks of HMW polymers, even for chemistries that would not fall within the polyvinyls sub-category, based on the properties of the new chemical substance compared to the PVC powder. Notwithstanding this, we recognize that data on a new chemical substance or an alternative analogue would take precedence over using one of these analogues as the default POD, if EPA concludes there are no study limitations on the new chemical substance or alternative analogue that would preclude the use of those data.

Due to the limited data on HMW polymers, available knowledge about inorganic PSPs was used to make inferences about HMW polymers. Compared to systemic effects, lung overload responses to inorganic PSPs show large variations in susceptibility between and among

mammalian species, with the rat being the only species to develop lung tumors [ADDIN EN.CITE
<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><
DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key
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le>Poorly Soluble Particles / Lung Overload</title></titles><pages>130,
http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-
Lung-Overload.pdf</pages><number>Technical Report No.
122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-
dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre
for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical
Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-
content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-
Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. This species-specific response has been explained by species differences in the accumulation of insoluble and respirable particles in the lungs, although cytotoxicity is also an issue with some inorganic PSPs (*e.g.*, crystalline silica). For example, humans are at least six times more resistant to attaining lung overload conditions than rats for the following reasons: human alveolar macrophages (AMs) are larger (*i.e.*, average volume = 4,990 μm^3) than rat AMs (*i.e.*, average volume = 1,166 μm^3); humans have a greater number of AMs (*i.e.*, average = 7.0×10^9) than rats (*i.e.*, average = 2.6×10^7); and human AMs patrol a smaller surface area (*i.e.*, average = 22,000 μm^2/AM) than

rat AMs (*i.e.*, average = 140,000 μm^2/AM) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, the site of retention for poorly soluble particles differs between rats and humans. Nikula *et al.* (2001) [ADDIN EN.CITE

<EndNote><Cite><Author>Nikula</Author><Year>2001</Year><RecNum>62</RecNum><DisplayText>[54]</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803440">62</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nikula, K. J.</author><author>Vallyathan, V.</author><author>Green, F. H.</author><author>Hahn, F. F.</author></authors></contributors><auth-address>Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, USA.</auth-address><titles><title>Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>311-8</pages><volume>109</volume><number>4</number><edition>2001/05/04</edition><keywords><keyword>Adult</keyword><keyword>Air Pollutants/*pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Coal</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Dust</keyword><keyword>Humans</keyword><keyword>*Inhalation Exposure</keyword><keyword>Lung/*chemistry</keyword><keyword>Macrophages, Alveolar</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>*Mining</keyword><keyword>*Occupational

Exposure</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Vehicle Emissions/*analysis</keyword></keywords><dates><year>2001</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765</isbn><accession-num>11335177</accession-num><urls></urls><custom2>PMC1240269</custom2><electronic-resource-num>10.1289/ehp.01109311</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] showed that “the relative amounts of intraluminal and interstitial particle load differ markedly between rats and humans with particles being found predominantly in the interstitium in man and intra-luminarly in rats.” In rats, accumulation of particulate matter in the intraluminal space leads to adverse “alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses” [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>].

As noted previously, EPA generally uses the polyvinyls sub-category analogue (*i.e.*, PVC powder) POD of 3.3 mg/m^3 for evaluating new chemical substances that may present a lung overload hazard when the chemical properties are comparable between the new chemical substance and the PVC powder. The polyvinyls sub-category POD is then subject to established EPA dosimetry adjustment. Each of these approaches is discussed below. These dosimetric adjustments may also be applied to the polyacrylates/methacrylates sub-category analogue (9000 Toner), as well as to data on new chemical substances or other potential analogues that fit within the chemical boundaries for this category.

As shown in [REF _Ref519678474 \h * MERGEFORMAT], the RDDRs for the PVC powder ranged from 0.501 in the pulmonary region (PU) up to 2.248 in the tracheobronchial (TB) region. Since the effects occurred in the PU region, the PU RDDR was used for deriving a POD_{HEC}, as follows:

Commented [JA35]: DEFINE what SA values used to compute

$$POD_{HEC} = POD \times RDDR_{PU}$$

or

$$POD_{HEC} = 3.3\ mg/m^3 \times 0.5 = 1.65\ mg/m^3$$

Table [SEQ Table * ARABIC]. Deposition~~al~~ fractions and RDDRs for rats and humans.[a]

SPECIES	Extrathoracic (ET)		Tracheobronchial (TB)		Pulmonary (PU)		Thoracic (TB + PU)		Total Respiratory Tract (RT)	
	Surface Area (cm^2)	Deposition~~al~~ Fraction	Surface Area (cm^2)	Deposition~~al~~ Fraction	Surface Area (m^2)	Deposition~~al~~ Fraction	Surface Area (m^2)	Deposition~~al~~ Fraction	Surface Area (m^2)	Deposition~~al~~ Fraction
Rat	15	0.33	22.5	0.068	0.34	0.061	0.342	0.129	0.344	0.459
Human	200	0.24	3200	0.059	54	0.267	54.32	0.125	54.34	0.566
RDD	0.075	1.373	0.007	1.15	0.006	0.229	0.006	1.028	0.006	0.811
RDDR	0.252		2.248		**0.501**		0.863		1.763	

[a] Input~~ted~~ values included: MMAD = 1.30; GSD = 2.07.
Value in bold is the RDDR chosen for calculation of the HEC.

Commented [JA36]: Correct term is DEPOSITION

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Commented [JA37]: WHAT DENSITY? PRESUMABLY THE SAME AS USED IN MPPD.

In comparison, the MPPD model was used to conduct simulations to predict retained mass burden in the PU region of female F344 rats exposed in the Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. The geometry model in the MPPD software for the Sprague-Dawley rat was used, but with the Agency default body weight (BW) of 229 grams for female F-344 rats in a chronic study [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-

Commented [ST38]: Section new based on parts of the write up that Owen and Annie developed. The remaining sections of the write up are in the Supporting File.

Commented [JA39]: Still question why MPPD not used for BOTH deposition and retained dose metrics.

type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD software internally scales ventilation parameters and respiratory volumes based on BW, so this resulted in tidal volume (V_T) of 1.54, a breathing frequency of 166 bpm, functional residual capacity (FRC) of 3.01 mL, and an upper respiratory tract (URT) volume of 0.34 mL. The 229 g rat PU surface area is predicted to be 1997 cm^2. The particle MMAD, GSD of the particle size distribution, and its density were: 1.3 µm, 2.07, and 1.3 g/cm^3, respectively. The regimen and duration of the nose-only exposure in the Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust

overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study was 5 h/d and 5 d/w for 8 months and was used in the simulation. We note that there were discrepancies in the reported duration of exposure of 7 months versus 8 months in Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. However, the Bellmann *et al*.

(1986) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1986</Year><RecNum>77</RecNum><DisplayText>[55]</DisplayText><record><rec-number>77</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595887108">77</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author></authors></contributors><titles><title>The Effect of a "Nuisance" Dust Inhalation of Lung Clearance</title><secondary-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</secondary-title></titles><periodical><full-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</full-title></periodical><pages>209-211</pages><dates><year>1986</year></dates><urls></urls></record></Cite></EndNote>] abstract consistently reported an 8-month exposure duration; therefore, a duration of 8-months was used.

Using the above experimental conditions, the predicted retained mass in the PU region of F344 rats, shown in [REF _Ref46766078 \h * MERGEFORMAT], demonstrated the fit of the MPPD model to the experimental data reported by Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. Additional simulations were conducted using the same three exposure concentration as Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-

377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>], but the key input parameters for MMAD, GSD, and density were varied and bounded. Details on the additional simulations are provided under "Section 4 MPPD Modeling Outputs" of the Supporting Information file. These additional simulations reinforce that prediction of overload kinetics is specific to the particle physicochemical properties (size, distribution, density) and experimental regimen. Such simulation demonstrations can be useful to defining whether a given particle and exposure conditions achieve overload.

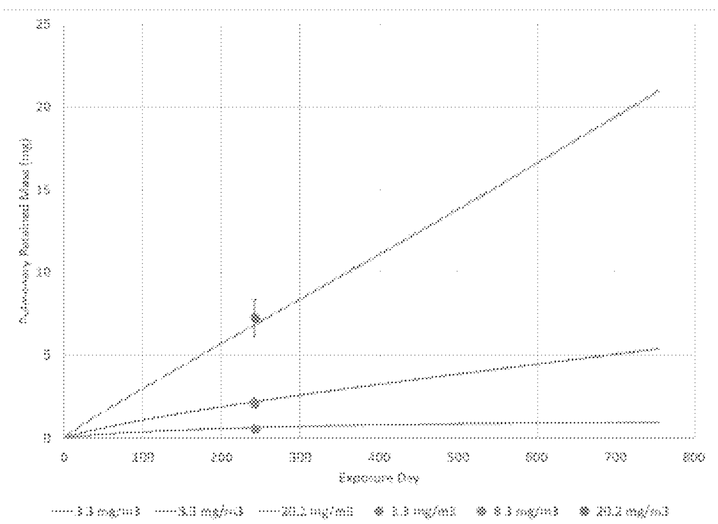

Figure [SEQ Figure * ARABIC]. MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle et al. (1990) [ADDIN EN.CITE

Commented [JA40]: REPLACE FIGURE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. Simulations were performed to characterize the 8-month study with a particle MMAD size of 1.3 µm, a GSD of 2.07, and a density of 1.3 g/cm^3 for three concentrations (3.3, 8.3, and 20.2 mg/m^3). Experimental data for PU burdens are shown as solid circles with standard deviation and the predictions as solid lines for different concentrations.

For extrapolation of the predicted rat retained PU mass to an HEC, human simulations were conducted for adult males with a V_T of 0.992 L and a breathing frequency of 21 bpm, or with 1.364 L and 33 bpm. These ventilatory values are from the ICRP (1994) [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><Dis

playText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key
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timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-
type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>
Human respiratory tract model for radiological protection. A report of a Task Group of the
International Commission on Radiological Protection</title><secondary-title>Ann
ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-
title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-
periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-
periodical><pages>1-482</pages><volume>24</volume><number>1-
3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keywo
rd>International Cooperation</keyword><keyword>*Models,
Theoretical</keyword><keyword>Neoplasms, Radiation-
Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation
Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation
Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory
System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract
Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</
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0146-6453</isbn><accession-
num>7726471</accession-num><urls><related-
urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-
urls></urls><remote-database-provider>NLM</remote-database-
provider><language>eng</language></record></Cite></EndNote>] and represent ventilation

associated with activity levels of either light exercise or heavy exercise for adult males. It should be noted that this combination of V_T and bpm for the light exercise ventilation input parameters are equivalent to the default minute ventilation value (V_E) found in [REF _Ref46666189 \h * MERGEFORMAT] of 1.25 m^3/hr. An occupational exposure duration of 40 years was simulated for the human predictions of retained mass in the PU region.

The dose metric used to operationally derive the HEC is the PU retained mass (mg) normalized to the PU surface area (SA) in cm^2 according to the established US EPA methods [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD model estimates a human pulmonary surface area of 66.3 m^2 for an 80 kg adult male. As shown in [REF _Ref46767442 \h * MERGEFORMAT], simulations were performed iteratively to arrive at an HEC that achieved the same internal dose metric (PU mass / PU SA) in humans as was achieved in rats under the experimental conditions reported by Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. As was shown in [REF _Ref46766078 \h * MERGEFORMAT], the predicted retained mass in the PU region corresponds well with the observed experimental data. The last two rows of [REF _Ref46767442 \h * MERGEFORMAT] demonstrate the difference in HEC value due to variation in ventilatory parameters associated with either light or heavy activity.

Table [SEQ Table * ARABIC]. MPPD predictions and HEC calculations for Muhle *et al.* (1990) study of F344 rats exposed to PVC with a particle MMAD of 1.3 μm, GSD of 2.07 and density of 1.3 gm / cm³.

Exposure Concentration (mg/m³)	**3.3**	**8.3**	**20.2**
Experimental Rat Retained PU Mass (mg)	0.56±0.16	2.09±0.29	7.24±1.10
Predicted Rat Retained PU Mass (mg)	0.63	2.21	6.88
Predicted Rat Retained PU Mass / PU SA (mg/m²)	2.8	10.5	36.3
Light Activity 40-Year HEC (mg/m³)	0.33	1.23	4.25
Heavy Activity 40-Year HEC (mg/m³)	0.14	0.53	1.84

HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

Category benchmark margin of exposure (MOE)

EPA currently applies a composite UF of 1,000 as the benchmark MOE for the PVC powder POD of 3.3 mg/m³. The composite UF consists of default values of 10 for UF_H, UF_A, and UF_L. This default approach was initially established as a conservative means of evaluating new chemistries on HMW polymers, which were anticipated to present a hazard concern for lung overload. However, several refinements to these values may be made, including reducing the TK and TD components of the UF_A value and reducing the UF_L. Dosimetric adjustments using the RDDR model or the MPPD model, as discussed above, may be applied to calculate a POD_{HEC}, thereby reducing the TK component of the UF_A to 1. Since lung overload is a chronic effect that is manifested primarily based on the retained dose in the PU region, the RDDR model is not necessarily the most appropriate for deriving a POD_{HEC}, given that deposition is a more relevant metric for short-term effects/exposures. However, the RDDR model was used to provide comparative estimates of the MOE to the other approaches versus the respective benchmark

Commented [JA41]: This is confusing. Wasn't the 3.3 mg/m3 just derived herein? And why wouldn't this be the HEC??

MOE, given that the RDDR model~~approach~~ is recommended in EPA guidance as the default for quantifying POD_{HECs} for particles. For the TD component, a reduced value of 1 may be applied based on the proposal from the ILSI Workshop Consensus Report on rat lung response to particle overload, which stated: “For both neoplastic and fibrogenic endpoints in the rat, associated with PSP exposures, the work group proposed that the TD component of the interspecies UF be reduced from a factor of 3 to 1, given that chronic active inflammation in the rat appears to be a more sensitive response than in other species, including humans” [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The UF_L may be reduced from 10 to 1 for the PVC powder analogue POD because this dose represented the point at which retardation of alveolar clearance started, based on the retained mass of about 0.5 mg/lung. This approach is consistent with EPA (2002) [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNot

Commented [JA42]: I don't follow this??

e>], which states that the UF_L “may be altered, depending on the magnitude and nature of the response at the LOAEL”. Further, the default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway. Based on the foregoing considerations, the following values are proposed for deriving the benchmark MOE for HMW polymers, which are generally applicable regardless of whether the POD is derived from an analogue or a new chemical substance.

UF_H = 10: The default value of 10 should be applied, unless there are human data showing which age groups or time periods are the most sensitive to lung overload. This approach is consistent with EPA’s guidance for reducing the default UF_H [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

UF_A = 3 or 1: A reduced value of 1 should be applied for the TD component based on consideration ~~the proposal~~ documented by Olin (2000). In addition, if the data are amenable for deriving a POD_{HEC}, the dosimetric adjustment for the TK component further supports reducing this UF [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

UF_L = 10 or 1: A value of 1 should be applied when the POD is based on a study NOAEC or when BMD modeling is applied to derive a BMCL, per EPA guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote

>]. The default value of 10 should be applied when the POD is based on a study LOAEC; however, a reduced value may be used, when for example, the LOAEC is based on key event 1 from the proposed adverse outcome pathway for PSPs. Reductions in the UF_L based on other key events should be made on a case-by-case basis and supported by discussion of the key event within the context of an established AOP.

The default and dosimetrically adjusted PODs and benchmark MOEs derived on new chemical substance risk assessments are used to inform risk management options for addressing potential risks. For example, the default POD of 3.3 mg/m^3 and benchmark MOE of 1,000 result in an MOE of 2.0E-01 that would require engineering controls and/or a respirator with an applied protection factor (APF) of 1,000. In comparison, when dosimetric adjustments are applied using the MPPD modeling outputs, the $POD_{HEC\text{-light activity}}$ of 0.33 mg/m^3 and refined benchmark MOE of 10 result in an MOE 1.7, which indicates that engineering controls and/or a respirator with an APF of 10 would be required.

Uncertainties and Limitations

The available toxicological studies for HMW polymers lack data on materials with molecular weights < 70,000 Daltons [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>63</RecNum><DisplayText>[57]</DisplayText><record><rec-number>63</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803909">63</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>H

igh Molecular Weight Polymers in the New Chemicals Program</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/high-molecular-weight-polymers-new</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. In addition, the following uncertainties and study limitations were noted, that if known, may serve to refine the boundaries for this category:

- Physicochemical properties can influence deposition of inhaled particles (*e.g.*, particle size, distribution, density, and hygroscopicity) while~~and~~ ~~biopersistence and bioreactivity~~ ~~(*e.g.*,~~ solubility, surface chemistry, and composition determine biopersistence and bioreactivity ~~)~~ and thereby impact clearance and retention. However, the available studies of test materials in this category are generally missing information on these properties, with the exception of particle size.
- Information on molecular weight was not reported for test materials used in the studies of the PVC powder [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

Commented [JA43]: These are not PC properties – solubility, surface chemistry and composition are. Reworded for accuracy.

Commented [JA44]: These are not PC properties – solubility, surface chemistry and composition are. Reworded for accuracy.

timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>].

- The test materials administered in the 9000 toner studies [ADDIN EN.CITE ADDIN EN.CITE.DATA] included colorant materials (predominantly carbon black) at up to 10%, and the influence of these colorants on the observed effects is unknown.
- The PODs summarized in [REF _Ref46678612 \h * MERGEFORMAT] for the HMW polymers were reported on a mass/volume basis. However, there is evidence that number of particles, particle volume, and/or volume of particles retained in the lung can influence the threshold at which lung overload conditions occur [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Data emerging on nanomaterials and ambient ultrafine particles also increasingly suggest surface area may determine toxicity. Thus, different internal dose metrics should be explored. This can be done readily with dosimetry models as described. ~~Thus, particle density may be an important consideration in identifying a~~

Commented [JA45]: Density has NOTHING to do with calculation of particle volume!! This needs CORRECTION. Particle volume and surface area are directly calculated from MMAD and GSD assuming lognormal distribution.

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~~POD; however, the appropriate density metric and how density should be incorporated remain uncertain~~ ~~[ADDIN EN.CITE~~
~~<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]~~.

Commented [JA46]: ?? DENSITY is one of the main determinants (see Figure 6 in supplemental) and is a REQUIRED INPUT to both RDDR and MPPD models. CLARIFY

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- Particle morphology, reactive groups, and cytotoxicity can impede clearance pathways and induce other mechanisms of toxicity in rodents and humans. These factors include covalent binding to lung tissues, toxicity to clearance macrophages/cilia and particles lodging in pulmonary tissues which may not be considered in aerodynamic models. An *in vitro* macrophage clearance assay utilizing human or primate cells and rat cells would be potentially useful information to determine whether new chemistries fall within or outside the boundaries for this category.

An additional, important consideration pertains to the uncertainty associated with the human relevance of lung tumors observed in rats exposed to PSPs. ~~The available data clearly demonstrate that the rat is a sensitive model for non-neoplastic pulmonary effects following repeated exposure to PSPs, which have also been shown to occur in occupational cohorts (*e.g.*, coal miners).~~ The rat ~~also~~ appears to be unique among species with regard to carcinogenesis in the lung due to particle overload. Lung tumors following chronic exposure to PSPs have been reported in rats, but have not been reported in mice, hamster, non-human primates, or humans [ADDIN EN.CITE
<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-

Commented [JA47]: I am not aware of this. Lung tumors yes. Other toxicity not well established.

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content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. Despite the uncertainty in the carcinogenicity of inhaled PSPs, the rat model remains a useful model for lung overload because it is a sensitive model for inflammatory response to PSPs, and because protecting against inflammation and proliferation may also protect against tumor formation [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Tiered-testing Strategy

The POD and benchmark MOE derived herein provide an analogue/read-across approach for assessing new chemical substances that fit within the chemical category boundaries for HMW polymers, also defined herein. As with any analogue read-across, assessors must carefully consider the comparability of the new chemical substance to the analogue or another acceptable toxicological analogue; this framework provides specific criteria for evaluating whether a new chemical substance "fits" into the HMW polymer category (*i.e.*, not chemically reactive, insoluble in water, not expected to be directly cytotoxic, not expected to release toxic degradates). Additionally, we demonstrate the utility of dosimetry modeling to inform evaluation or experimental design.

When information is not available to evaluate whether the new chemical substance fits within the category boundaries and the analogue is appropriate for use in a risk assessment, testing should be performed to aid with refining the evaluation of new chemistries that are anticipated to present a potential lung overload hazard. A tiered-testing strategy that is consistent with the reduced vertebrate testing requirements under the amended TSCA is provided. Though this strategy does not completely exclude vertebrate testing, it maximizes the use of NAMs for determining whether vertebrate testing should be considered. This strategy incorporates *in chemico* and/or *in vitro* characterization of the chemical substance in Tier I (*e.g.*, particle size distribution, density, reactivity, and biosolubility measurements). For substances that have particles in the respirable range, are non-reactive, and are not biosoluble, computational dosimetry screening is included under Tier II to determine whether the HMW polymer is estimated to exceed the clearance t½ in the rat or demonstrate overload under anticipated use conditions. If the HMW polymer is expected to exceed the clearance t½ in the rat, then risk management options or strategic *in vivo* testing is proposed as a final option under Tier III.

Tier I

- **Particle Size Distribution** or Aerosolized Droplet Size of particle in use (*i.e.*, cascade impactor, laser methods, *e.g.*, OECD TG 110 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>64</RecNum><DisplayText>[59]</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595804668">64</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Particle Size Distribution/Fibre Length and Diameter Distributions</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for

Testing of Chemicals</full-title></periodical><pages>13, https://www.oecd-ilibrary.org/environment/test-no-110-particle-size-distribution-fibre-length-and-diameter-distributions_9789264069688-en</pages><volume>110</volume><dates><year>1981</year></dates><urls></urls></record></Cite></EndNote>], OPPTS 830.7520 [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>65</RecNum><DisplayText>[60]</DisplayText><record><rec-number>65</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595804850">65</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Particle Size, Fiber Length, and Diameter Distribution</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>13, https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-830-product-properties-test-guidelines</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]) of the new chemical substance during specific use(s) (*i.e.*, depending on the intended or known uses of the chemical substances, particle size distribution may need to be tested under more than one use scenario)

- If the % of respirable particles (*i.e.*, ≤ 10 µm) is less than 1 wt% under the conditions of use, or following transport, stop at Tier I.
- If the % of respirable particles (*i.e.*, ≤ 10 µm) is greater than 1 wt% under the conditions of use, or if respirable particles are anticipated or shown to be generated following transport (> 1%), then proceed with reactivity testing, if needed, or biosolubility testing.

- **Reactivity**
  - If the HMW polymer is a potential concern for reactivity, based on function or other information (*e.g.*, does not meet the E1 FG/FGEW criteria), reactivity should be assessed using an *in vitro* method, preferably discussed with EPA in a pre-notice consultation meeting and prior to study initiation. The assay developed by Wiemann *et al.* (2013) [ADDIN EN.CITE ADDIN EN.CITE.DATA] provides a potential option; however, there are caveats with its use, such as not being validated and uncertainty with whether the test method could be used with HMW polymers, underscoring the recommendation to consult with EPA prior to testing using this method or other test methods.
  - If substance is "reactive" (*e.g.*, does not met the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, it would be excluded from the HMW polymer category. If evidence indicates the substance is "non-reactive" (*e.g.*, it does meet the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, then proceed to biosolubility testing.

- **Biosolubility Testing**
    - Solubility in Gamble's solution (*e.g.*, ECETOC, 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]), simulated epithelial lung fluid (SELF) (*e.g.*, Boisa *et al*. 2014 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and/or phagolysosomal simulant fluid (*e.g.*, BAUA, 2017 [ADDIN EN.CITE

<EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57 </RecNum><DisplayText>[30]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>])

- Employ a simple exponential decay model to predict the dissolution half-life: $P(t)=P0e^{-rt}$, where: P(t) = the amount of some quantity at time t; P0 = initial amount at time t = 0; r = the decay rate; t = time

The exponential decay function is the solution to the first order reaction equation, assuming a constant decay rate, r:

$$\frac{dP(t)}{dt} = -rP(t), P(0) = P_0$$

First order kinetics are used as the basis for lung clearance rates including dissolution and absorption into blood [ADDIN EN.CITE ADDIN EN.CITE.DATA].

- If the solubility data indicate a dissolution rate (*i.e.*, 100 mg/L/day or 72 mg/day) higher than the daily occupational exposure estimate (*e.g.*, default PDR of 50 mg/day), then stop at Tier I.
- If the solubility data indicate a dissolution rate lower than the daily occupational exposure estimate, then proceed with Tier II testing.

If the % of respirable particles is > 1 wt%, the HMW polymer is non-reactive, and the HMW polymer has a dissolution rate that is lower than the estimated daily occupational exposure estimate, proceed to Tier II.

Tier II

- Perform computational modeling (*e.g.*, MPPD) including the effect of dissolution to predict deposition, clearance, and lung burden for a simulated chronic rat exposure (See, *e.g.*, Ladics *et al.*, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[19]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle

Commented [JA48]: ?? DIFFICULT TO MODIFY THE AI COMPONENTS OF MPPD, plus overload pertains to INSOLUBLE PARTICLES.

Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]). If dissolution data are not available, assume the test article is a poorly soluble particle (PSP).

- If the clearance t½ is less than 60 days, stop at Tier II.

Commented [JA49]: ?? WHY NOT PERFORM SIMULATIONS AS WE DID TO DEMONSTRATE IF OVERLOAD OCCURS OR NOT?? Isn't that what you asked us to do?

If the clearance t½ is greater than that for PSPs in the rat (*i.e.*, 60 days) [ADDIN EN.CITE <EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[36]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-title></periodical><pages>123-135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>], consider risk management options (*e.g.*, engineering controls and personal protective equipment) or proceed to Tier III.

Tier III

- Strategic *in vivo* testing should be considered, albeit on a case-by-case basis. When performed, the testing should include:
  - MPPD simulations to predict for the specific particle size, distribution, and density of the PVC in question at what exposure level overload is likely to occur.
  - Exposure concentrations high enough to demonstrate impaired pulmonary clearance of particles and lead to an "overload" condition. It has been shown that in rats impaired clearance starts when phagocytized particle volume exceeds 6% of normal alveolar macrophage volume and clearance stops altogether when phagocytized volume reaches 60% of normal macrophage volume (See, *e.g.*, Borm *et al.*, 2015 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and
  - Special attention to pulmonary function tests; blood oxygen (pO_2); lung burden measurements and lung clearance kinetics; collection of BALF for assessment of marker enzyme activities, total protein content, and cell counts; lung retention and clearance; lung weight; and lung histopathology (inflammation and cell proliferation). It is not necessary to evaluate internal organs. OECD TG 413 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>71</RecNum><DisplayText>[64]</DisplayText><record><rec-number>71</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838832">71</key></foreign-keys><ref-type name="Journal Article">17</ref-

Commented [JA50]: WHY would you use ONE simulation (Muhle) to predict a category when it is easy to TAILOR SPECIFICALLY to unknown in question??

Commented [JA51]: Don't you want OTHERS to NOT be at overload condition??

type><contributors><authors><author>OECD</author></authors></contributors
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urls></record></Cite></EndNote>] and OECD GD 39 [ADDIN EN.CITE
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><titles><title>Guidance Document on Inhalation Toxicity Studies, Series on
Testing and Assessment (Second Edition)</title><secondary-title>Environment
Directorate Joint Meeting of the Chemicals Committee and the Working Party on
Chemicals, Pesticides and Biotechnology</secondary-
title></titles><periodical><full-title>Environment Directorate Joint Meeting of
the Chemicals Committee and the Working Party on Chemicals, Pesticides and
Biotechnology</full-title></periodical><pages>106,

https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&doclanguage=en</pages><volume>ENV/JM/MONO(2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] should be consulted, given that the 90-day subchronic inhalation toxicity study in rats (OECD 413) with a 60-day recovery period is sufficient for identifying lung overload for PSPs in this species [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

CONCLUSIONS

The MPPD software provides for a straightforward approach to predict when overload might occur in the experimental species, perform interspecies extrapolation to HEC estimates, and inform inferences for human health risk evaluation. Concentrations at which overload was not achieved in the rat are relevant to human assessment, as are other endpoints other than tumors at overload. Simulations would also be most useful to design of experiments before costly investments in inhalation studies are made and may also help to reduce and refine the number of animals used.

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ASSOCIATED CONTENT

Supporting Information.

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. Experimental Animal Inhalation Studies on HMW Polymers

Section 3. Benchmark Dose (BMD) Modeling Outputs

Section 4: MPPD Modeling Retained Dose Predictions and HEC Calculations~~Outputs~~

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally. (match statement to author names with a symbol)

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Notes

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

ACKNOWLEDGMENT

Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).

REFERENCES

[ADDIN EN.REFLIST]

Message

From: Marrapese, Martha [MMarrapese@wileyrein.com]
Sent: 9/25/2019 6:13:19 PM
To: Henry, Tala [Henry.Tala@epa.gov]
CC: Heinzman, Tracy [THeinzman@wileyrein.com]
Subject: Presentation and Suggestions
Attachments: Ski Wax Industry Presentation.pptx; SIA TSCA Presentation DRAFT_0925 DRAFT With EPA slides.pptx

Dear Tala,

The deck you sent looks fantastic in terms of the information on PFAS and the level of detail on new chemical reviews.

Since we all need to come in around 20-25 minutes in our segments, I have attached some suggestions that would bring your 30 slides to 22:

Ex. 5 Attorney Work Product (AWP)

The second attachment to this email is the entire presentation as it would look with these suggestions included. Please edit as you see fit (add slides back in or whatever you need to do) and get back to me later this afternoon?

Thank you very much again for working on this. It is very, very important for the industry to hear from EPA.

Sincerely, Martha

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sia Snowsports Industries America

The U.S. EPA, PFAS, and the Ski Wax Industry

What You Need to Know

September 26, 2019

Agenda for Today's Presentation

- Background – EPA's Review of PFAS and How Chemical Substances in Ski Wax Are Regulated Under the Toxic Substances Control Act (TSCA)

  Dr. Tala Henry, US EPA

- Specific Requirements and Compliance Challenges for Ski Wax Companies under TSCA

  Martha Marrapese, Wiley Rein LLP

- What's At Stake – EPA Enforcement and Consequences of Non-Compliance

  Tracy Heinzman, Wiley Rein LLP

- Questions

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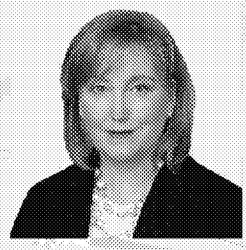

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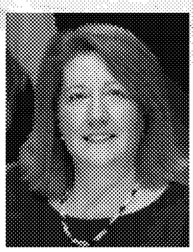
EPA's Review of PFAS and How Chemical Substances in Ski Wax Are Regulated Under the Toxic Substances Control Act (TSCA)



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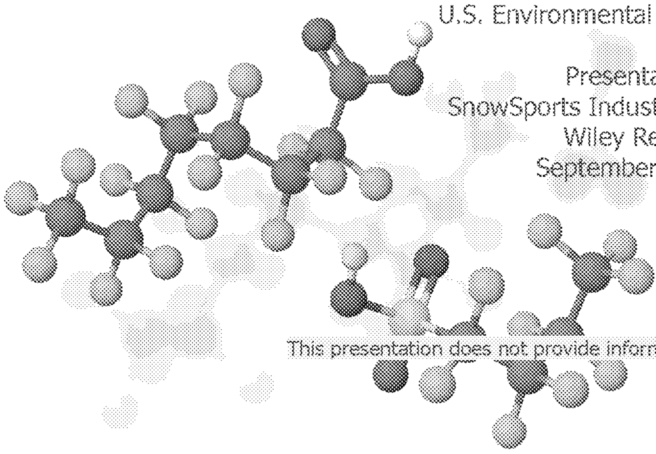
TOXIC SUBSANCES CONTROL ACT (TSCA) & PFAS

Tala Henry, PhD
Deputy Director for Programs
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency

Presentation to
SnowSports Industries of America &
Wiley Rein, LLC
September 26, 2019



This presentation does not provide information regarding compliance with TSCA.

EPA United States Environmental Protection Agency

TSCA: New Chemicals

- TSCA Section 2(b)(3):
  - Authority over chemical substances and mixtures should be exercised in such a manner *as not to impede unduly or create unnecessary economic barriers to technological innovation.*
  - While fulfilling the primary purpose of this Act to assure that such innovation and commerce in such chemical substances and mixtures *do not present an unreasonable risk of injury to health or the environment.*

Overview of New Chemicals Program

- Functions as a "gatekeeper" to help manage the potential risk to human health and the environment from chemicals new to the marketplace.

- Anyone who plans to manufacture (or import) a new chemical substance must provide EPA with notice - a Premanufacture Notice (PMN)

- EPA *must review* and evaluate new chemicals (or significant new uses of existing chemicals) and make an affirmative finding before those chemicals can enter the market

- Review must be completed within 90 days, with ability to extend 90 days

- If risks are identified, EPA *must* impose restrictions or prohibitions on the manufacturing, processing or use of the chemical to ensure the risks are mitigated

Exemptions from PMNs

- **Exemption Application Not Required for:**
  - R&D Chemicals
  - Exempted Polymers of Low Concern (only annual reporting)
- **Submission of Exemption Application Required:**
  - Low Volume (≤10,000 Kg/Yr) - 30 Day Review
  - Low Release/Exposure (LOREX) - 30 Day Review
  - Test Market Exemption (TME) - 45 Day Review
  - TSCA Experimental Release Application – 60 Day Review
  - Tier I and Tier 2 Biotechnology Exemptions
- For all exemption applications, EPA assesses whether the manufacture, processing, distribution in commerce, use or disposal of the substance will present an unreasonable risk to human health or the environment.

New Chemical Assessments

- New chemicals determinations are made using a risk-based approach, taking into account both hazard and exposure, under the substance's conditions of use (intended, known and reasonably foreseen).

- EPA assesses health and environmental hazards and exposures to:
  - multiple populations of humans: workers, consumers and general population, including susceptible subpopulations, e.g. different age groups of the general population)
  - the environment (e.g., primarily aquatic environment).

- Data required to be submitted with a new chemical (PMN) under TSCA is limited:
  - Details about how the chemical with be manufactured, processed and used
  - Only test data (e.g., fate tests, toxicity tests, etc.) that already exists; no new testing is required to be conducted for the submission.

- Therefore, EPA relies on predictive assessment methods, databases, and tools and models to evaluate chemicals throughout their lifecycle, i.e., manufacture, processing, distribution, use and disposal.

Types of Determinations under TSCA Section 5

Presents an Unreasonable Risk

- Section 5(f) order: Restriction/prohibition of manufacturing, processing, or distribution
- Section 6(a) Proposed Rule: Restriction/ prohibition of manufacturing, processing, distribution, or disposal

Not Likely to present an unreasonable risk

- Commercialization can commence after the determination is made
- Section 5(g) – Statement in the FR

Information is insufficient to permit a reasoned evaluation of the risk

- Section 5(e) – regulation pending more information
- Section 5(e) order

Insufficient information to permit a reasoned evaluation and **may present** unreasonable risk

- Section 5(e) – regulation pending more information
- Section 5(e) order

Significant New Use Rules (SNURs)

- A SNUR is a rule that identifies a potential new use of a chemical as a "significant new use."

- A manufacturer or processor intending to commence a significant new use must first submit to EPA a Significant New Use Notice (SNUN), and EPA must review and approve the use described in the SNUN before the company may commence manufacture or processing.

- TSCA authorizes EPA to propose or issue a SNUR for a chemical substance at any time, including during review of a section 5 notice for the chemical substance.

PFAS Activities under TSCA

United States Environmental Protection Agency

What are PFAS?

- Per- and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals that have been in use since the 1940s.
- There are many PFAS chemicals, including the chemicals perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and GenX chemicals (HFPO dimer acid and its potassium salt).

EPA United States Environmental Protection Agency

What are PFAS?

- Due to their strong carbon-fluorine bonds, many PFAS can be very persistent in the environment with degradation periods of years, decades, or longer under natural conditions.

- Two of the most studied PFAS are Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS).

Where are PFAS found?

- PFAS are (or have been) found in a wide array of consumer products like cookware, food packaging, and stain and water repellants used in fabrics, carpets and outerwear.
- PFAS manufacturing and processing facilities, and airports and military installations that use firefighting foams which contain PFAS.

PFAS and TSCA

- 1,223 PFAS chemicals have been identified as being on the TSCA Inventory historically.

- There are 602 PFAS chemicals reported as active in commerce in the ten years prior to June 22, 2016.

PFAS and TSCA

TSCA TOOLS

Voluntary Agreements	Regulatory			
2010/15 PFOA Stewardship Program	Manage Alternatives - New Chemicals Program	Significant New Use Rules (SNURs)	Toxics Release Inventory (TRI)	TSCA Section 6 as Potential Tool for Risk Management

PFAS and TSCA

- **PFOS Phaseout**
  - EPA worked with industry to phase out production of PFOS and related chemicals between 2000 to 2002
- **2010/2015 PFOA Stewardship Program**
  - In 2006, EPA, in cooperation with eight major companies that manufactured and/or processed long-chain PFAS, launched the 2010/2015 PFOA Stewardship Program with the goal of eliminating long-chain PFAS from emissions and products by 2015
    - Arkema, Asahi Glass Company, BASF Corporation (formerly Ciba Specialty Chemicals Corporation), Clariant, Daikin, 3M/Dyneon, Chemours (formerly DuPont), and Solvay Solexis
  - All participating companies have met the PFOA Stewardship Program goals
  - Some companies that were not part of the PFOA Stewardship Program continue to produce/import and use PFOA and other long-chain PFAS that were phased out by others under the program

PFAS and TSCA

- **TSCA Activities for Existing PFAS Chemicals**
  - 2002: SNUR on 13 perfluoroalkyl sulfonate chemicals (67 FR 11008)
  - 2002: SNUR on 75 perfluoroalkyl sulfonate chemicals (67 FR 72854)
  - 2003: Enforceable Consent Agreement (ECA) Process (68 FR 18626) to develop data on use and production, exposure, toxicity, pharmacokinetics, and monitoring on long-chain PFAS
  - 2007: SNUR on 183 perfluoroalkyl sulfonate chemicals (72 FR 57222)
  - 2010: Premanufacture Notification Exemption for Polymers: Amendment of Polymer Exemption Rule to Exclude Certain Perfluorinated Polymers (75 FR 4295) revoking PFAS polymers from exemption under the polymer exemption rule
  - 2013: SNUR on long-chain perfluoroalkyl carboxylate chemical substances (LCPFAC) as part of carpets or carpet treatment products (78 FR 62443)
  - 2015: Proposed SNUR on LCPFAC and perfluoroalkyl sulfonate chemicals (80 FR 2885) to support the voluntary PFOA Stewardship Program phaseout of long-chain PFAS

The significant new uses for perfluoroalkyl sulfonates in the 2002 and 2007 SNURs (CFR §721.9582):
Any manufacture or import for any use
Manufacture or import for the following specific uses is not considered as a significant new use subject to reporting (because these are ongoing uses and therefore not "new"):
Use as an anti-erosion additive in fire-resistant phosphate ester aviation hydraulic fluids
Use as a component of a photoresist substance, including a photo acid generator or surfactant, or as a component of an anti-reflective coating, used in a photomicrolithography process to produce semiconductors or similar components of electronic or other miniaturized devices
Use in coating for surface tension, static discharge, and adhesion control for analog and digital imaging films, papers, and printing plates, or as a surfactant in mixtures used to process imaging films
Use as an intermediate only to produce other chemical substances to be used solely for all of the uses listed above
Manufacture or import of tetraethylammonium perfluorooctanesulfonate (CAS No. 56773-42-3) for use as a fume/mist suppressant in metal finishing and plating baths (e.g., hard chrome plating; decorative chromium plating; chromic acid anodizing; nickel, cadmium, or lead plating; metal plating on plastics; and alkaline zinc plating)
Manufacture or import of a few perfluoroalkyl sulfonates for use as a component of an etchant, including a surfactant or fume suppressant, used in the plating process to produce electronic devices

The significant new uses for LCPFAC in the 2013 SNUR (CFR §721.10536):
Manufacture (including import) or processing for use as part of carpets or to treat carpets (e.g., for use in the carpet aftercare market)
Manufacture (including import) or processing of CAS No. 68412-68-0 and CAS No. 68412-69-1 for use as a surfactant in aftermarket carpet cleaning products is not be considered a significant new use subject to reporting

PFAS and TSCA

- In 2015, EPA published the proposed SNUR on LCPFAC to ensure that LCPFAC chemicals that have been phased out under the 2010/2015 PFOA Stewardship Program do not re-enter the marketplace without review
  - EPA intends to issue a supplemental SNUR for the import of certain LCPFAC chemical substances as part of categories of certain articles following changes to TSCA brought about by the Frank R. Lautenberg Chemical Safety for the 21st Century Act in June 2016 (RIN 2070-AJ99)

PFAS Background and Action Plan

EPA United States Environmental Protection Agency

Action Plan Background

- EPA convened a two-day National Leadership Summit on PFAS in Washington, D.C.
- Following the Summit, the agency hosted a series of visits during the summer of 2018 in communities directly impacted by PFAS where EPA interacted with more than 1,000 people.
- The EPA's PFAS Action Plan was developed based on feedback from these events in addition to information received from approximately 120,000 comments submitted to the public docket.

Action Plan Purpose

- Provides EPA's first multi-media, multi-program, national research, management and risk communication plan to address a challenge like PFAS.
- Responds to the extensive public input the agency has received over the past year during the PFAS National Leadership Summit, multiple community engagements, and through the public docket.
- As a result of this unprecedented outreach, the Action Plan provides the necessary tools to assist states, tribes, and communities in addressing PFAS.

Highlighted Actions

- The EPA is committed to following the MCL rulemaking process as established by SDWA for water treatment and EPA will propose nationwide drinking water monitoring for PFAS under the next UCMR monitoring cycle.
- The EPA is initiating the regulatory development process for listing certain PFAS as hazardous substances.
- The EPA is rapidly expanding the scientific foundation for understanding and managing risk from PFAS.
- The EPA uses enforcement tools, when appropriate, to address PFAS exposure in the environment and assist states in enforcement activities.

Highlighted Actions

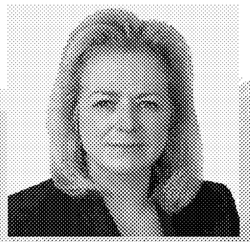
Toxics

- The EPA is considering the addition of PFAS chemicals to the Toxics Release Inventory
- EPA is issuing a supplemental proposal to guard against the unreviewed reintroduction and new use, through domestic production or import, of certain PFAS chemicals in the United States.

The EPA will provide updates on actions outlined in the plan on the Agency's website.

Thank you

Specific Requirements and Compliance Challenges for Ski Wax Companies under TSCA



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sia Snowsports Industries America

Enforcement & the Ski Wax Industry

- Timeline:
  - 2017, EPA began issuing subpoenas demanding information on the ingredients contained in ski wax products.
  - Our understanding is that the investigation began because the agency determined that these products can contain PFAS.
  - During the last two seasons, EPA has issued subpoenas to importers, distributors, and manufacturers of ski wax suppliers.
  - Let to sales disruption and widespread industry speculation.
  - EPA's investigation and enforcement actions are on-going.
  - Part of an agency-wide initiative to regulate PFAS that is getting national attention.
  - This presentation is designed to explain what has been happening.

Wiley Rein

The Basis for EPA's Investigation of PFAS in Ski Wax is the Law Known as "TSCA"

- **The Toxic Substances Control Act** – TSCA
- The law applies to **<u>all ski wax products</u>**:
  - Glide wax, klisters, kick wax, grip wax, etc.
  - Hard wax, sprays, liquids
  - Fluoro and Non-fluoro
  - Nordic, Alpine
  - Skis, boards, sleds, boats
  - Other products like wax cleaners

TSCA was recently updated in 2016

Wiley Rein LLP

The basis for EPA's enforcement is a law called the Toxic Substances Control Act. TSCA applies to all ski wax products. To be clear, TSCA is not a new law. It was part of the USA's suite of major environmental statutes passed in the 1970s and 80s. The CAA was first updated in 1970, the CWA was passed in 1972, RCRA, our federal hazardous waste law, was passed the same year as TSCA in 1976, and our Superfund law was passed by Congress as CERCLA in 1980. In fact, TSCA has been around so long that Congress updated it in 2016! The changes have put more national attention on existing chemicals like PFAS and also require EPA to pay particular attention to the use of potentially harmful chemicals in consumer products.

Who Does EPA Regulate?

- **Not Just Ski Wax Importers!**
- The exact same rules apply to these types of ski wax businesses:
  - U.S. Subsidiary of an EU Company/importer
  - U.S. Distributor/importer
  - U.S. Manufacturer
  - U.S. Store selling its own private label wax whether manufactured here or abroad ("contract manufacturer")
- **If you are one of these entities, you are a chemical company and you have to act like one.**

Wiley Rein

As part of this presentation with SIA, we want to eliminate any misunderstanding about who in the ski wax industry needs to be concerned about complying with this law. If you think EPA does not regulate you because you do not import ski wax, think again. If you make it here, the law applies to you. TSCA's rules are the same for manufacturers and importers. The TSCA definition of a manufacturer includes importers.

Based on our understanding of how the ski wax industry operates in the US, the following companies are regulated in the same manner as a chemical company (LIST). The companies that are importing their ski wax have to know that all of the ingredients that they are bringing into the country are in compliance. In the same way, if you manufacture ski wax here, all of the ingredients you use to make the waxes need to be compliant with TSCA.

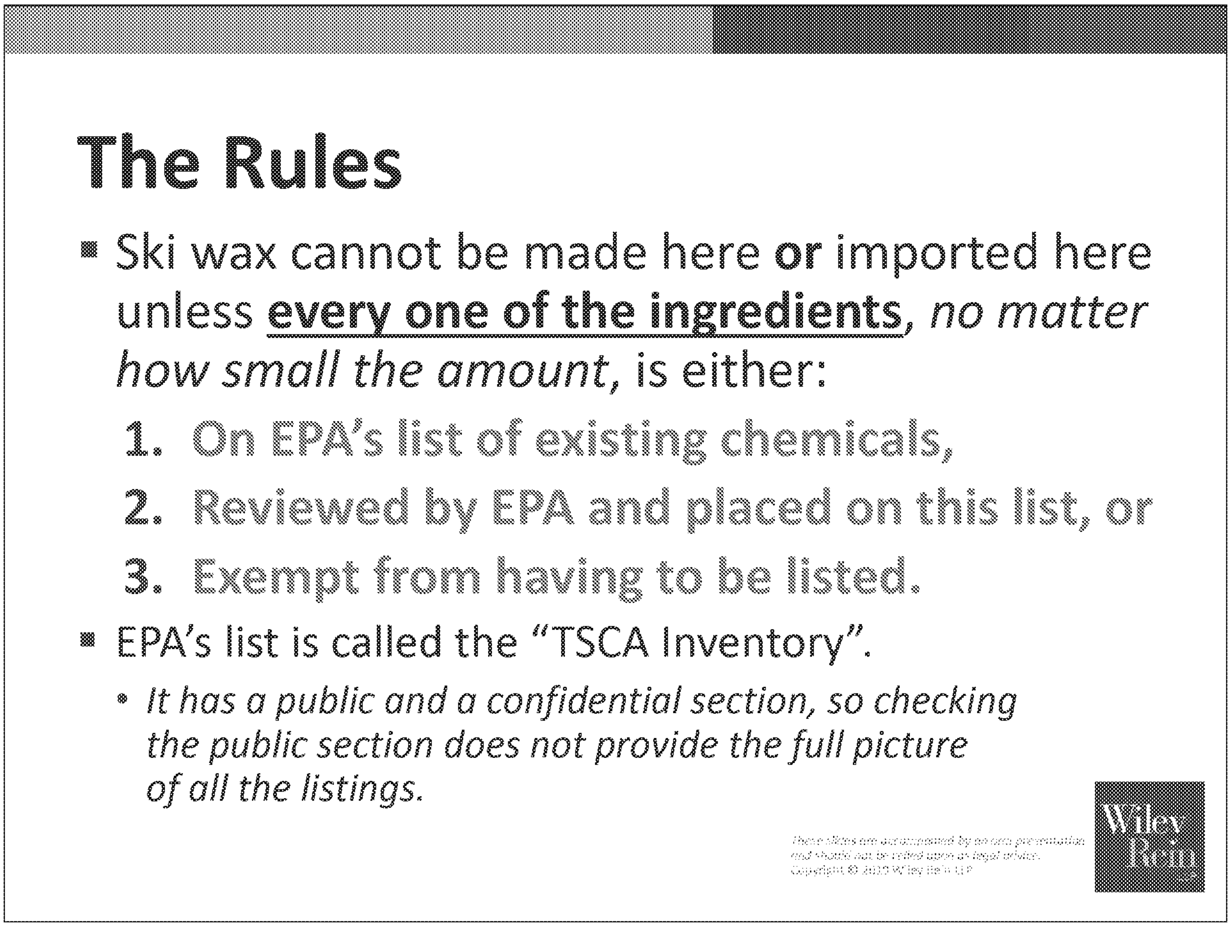
Every wax supplier must follow this law and keep proper records for at least 5 years of prior commercial activity to verify that you understand and are meeting your obligations. You are required by law to verify and document compliance whether or not EPA asks you for this information.

REACH Compliance ≠ TSCA Compliance

- TSCA compliance is **<u>not</u>** guaranteed by good standing under the European Union REACH Regulation.
  - The REACH exemption for small quantities of substances (<1,000 kg) is not available in the US.
  - REACH in 2020 DOES allow C8 to continue to be present in ski waxes a lower level. The C8 in a wax product may or may not be on the EPA's TSCA Inventory. This must be verified.

Another common misconception about TSCA among companies that do a lot of business with companies in the European Union is that if you comply in Europe you comply with the law here. That is not necessarily the case, especially when it comes to PFAS substances, fragrances and colors. Ski waxes only need a little of these materials, but the low volume exemption the Europeans use under REACH to comply does not apply here in the United States. Other examples in my experience include:
some PFAS chemicals may be on the EU list of approved substances but not on the EPA's approved list;
different chemical names can apply to qualify chemicals under REACH;
The EU may establish different safety levels that are not recognized by EPA, such as the one they have established for the PFOA degradation product of C8 perfluoros.

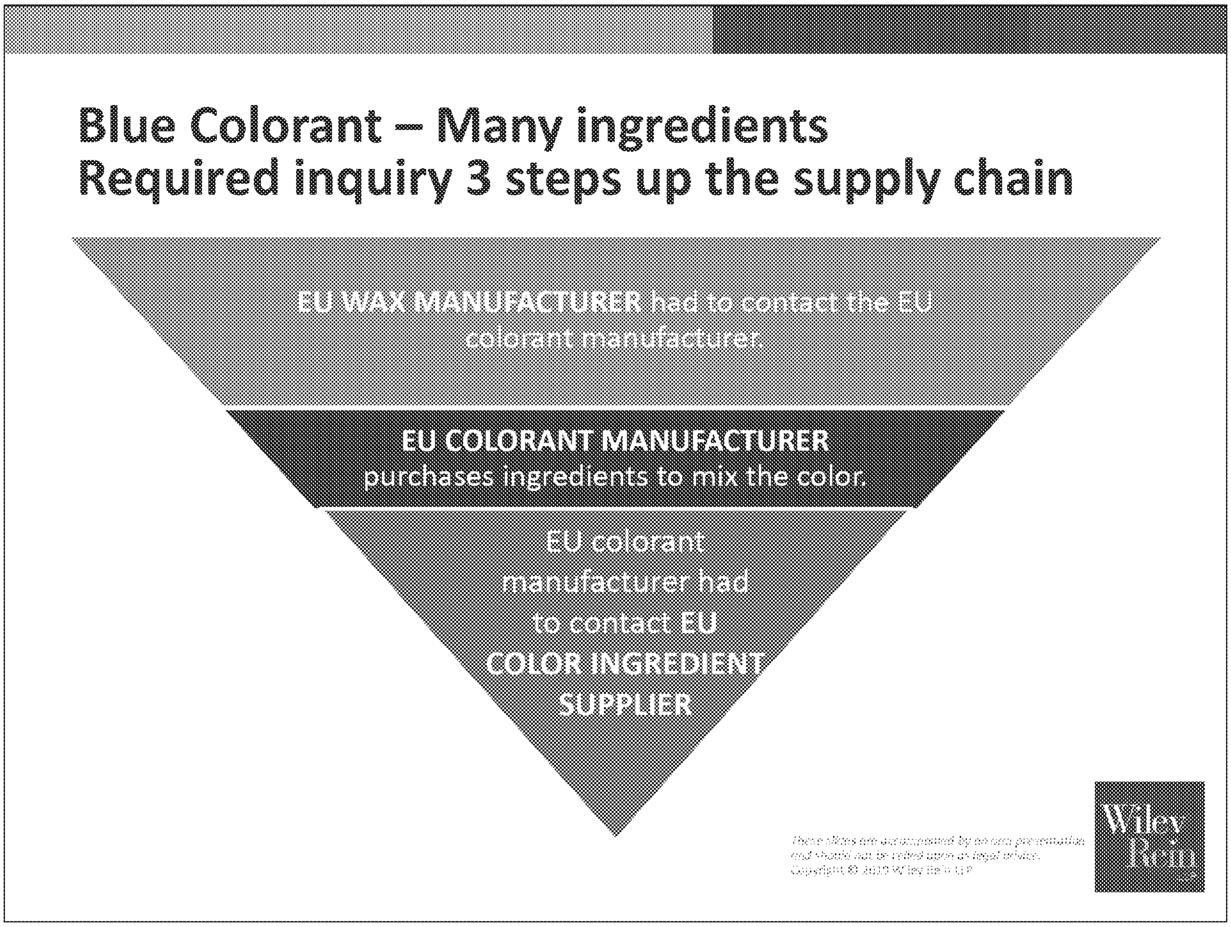
One more misconception to debunk here is that compliance with workplace safety requirements under OSHA or EU CLP means you comply with TSCA. These are two very different laws. It's true that TSCA and REACH allow the government to regulate chemicals in the workplace. Information from one may be useful for determining compliance with the other, but they are not the same at all.



What are the TSCA rules that apply equally to manufacturers and importers? First and foremost, ski wax cannot be made or brought into the country unless every one of the ingredients, no matter how small the amount, is either already on EPA's list of existing chemicals, reviewed by EPA and placed on this list, or exempt.

Exemptions are few and far between, so don't count on having one to bail you out. Most TSCA exemptions will not apply to the ingredients that are intentionally added to ski wax. EPA's low quantity exemption requires that you notify EPA and get the agency's approval before you import or manufacture the chemical.

Because a hard wax is melted during end use, the exemption for ingredients that are part of an article does not apply. The article has to keep its shape during end use, and because the hard wax is converted to a liquid when it is applied it does not qualify as an article per TSCA.



On this slide we have an example of the level of detailed review that is required. As everyone knows on this webinar, Ski wax is color coded. Yellow signals that a wax is suitable for use under warmer conditions, red is for around the freezing mark, with purple, blue and green signaling uses under increasingly cold conditions.

For the purpose of presenting this example, we were given permission to disclose that we have been assisting Swix Sport USA with their TSCA ingredient review. So, during that review, we looked at a blue colorant that is used in some of their waxes. It turns out from looking at the SDS and communicating with the supplier that this blue dye has a total of 19 different ingredients. Initially, some of them were identified as single chemicals and some were identified by trade names and were actually mixtures of two or more chemicals. To determine whether each ingredient in the dye was compliant with TSCA required working with the EU parent company's regulatory department, and going two more steps up the supply chain.

The SDS from the colorant manufacturer, which BRAV had, was a good start, but not sufficient to make a TSCA compliance determination. Why? Most SDSs do not list 100% of the formulation. Trade names mask mixtures, non-hazardous ingredients need not be disclosed, and even hazardous ingredients may be left off an SDS if they are below the 1% or 0.1% (in the case of carcinogens) threshold levels under OSHA HazCom and EU CLP workplace safety rules.

We had to ask BRAV Norway to work with us to contact the colorant manufacturer. That EU colorant manufacturer purchases ingredients to mix the color. Some of these ingredients are proprietary so the colorant manufacturer did not know what they were or their TSCA status. So, the EU colorant manufacturer had to contact its ingredient suppliers for the information we needed.

Fortunately, in this case all of the ingredients in the blue dye are on EPA's TSCA Inventory list. In another case, one of the fragrances used in a Swix wax had a similar number of ingredients, but we were not so lucky. In that case, the fragrance manufacturer's SDS did list 100% of the formulation with the formal chemical names and identifiers that we call Chemical Abstracts Service Registry Numbers (CASRN). But out of the multiple ingredients in the fragrance, only one was not on the EPA's list. Because of that one single chemical, the entire fragrance was not compliant and it is not used anymore in wax sold in the US.

If a chemical is not on EPA's list or exempt it is a "NEW CHEMICAL SUBSTANCE"

If a chemical substance is on the TSCA Chemical Substances Inventory ("**TSCA INVENTORY**"), the substance is an "existing" chemical substance in U.S. commerce.

A chemical substance that is not on the TSCA Inventory is a "**NEW CHEMICAL SUBSTANCE**."

A **NEW CHEMICAL SUBSTANCE** CANNOT BE MANUFACTURED, PROCESSED OR IMPORTED WITHOUT EPA REVIEW FIRST

A PMN is not required if the **NEW CHEMICAL SUBSTANCE** is exempted/excluded by TSCA.

A **NEW CHEMICAL SUBSTANCE** requires a premanufacture notification (PMN).

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Just to recap, we have been talking about finding chemical substances on EPA's list of approved substances, which is called the TSCA Inventory. If a chemical is not on this list, you cannot import any products that its in or make wax here with it unless EPA reviews and approves the chemical first.

More on the PMN Process

- PMNs are required for Manufacturers **<u>and</u>** Importers
- PMNs must be submitted at least 90 days before commencing non-exempt commercial activity
- EPA reviews PMNs for whether the substance presents an unreasonable risk to human health or the environment
  - Based on conditions of use
  - No consideration of cost or non-risk factors
  - Must include risk to susceptible populations
- EPA issues Significant New Use Rules (SNURs) to restrict uses of chemicals on the TSCA Inventory.
  - Many TSCA SNURs are final on the or proposed to restrict uses of PFAS chemistry

Wiley Rein

Again, the new chemical notification process applies to both manufacturers and importers. It applies to a company that contracts with another company to make a ski wax with the contracting company's name on it. The review process is extremely detailed, and frequently takes longer than 90 days. Certain chemistries including PFAS chemistry raise concerns of unreasonable risk during EPA reviews. When chemicals raise these concerns, it is difficult to get them approved and it may not even be possible to get them approved. In other cases, their use will be highly regulated and limited as a condition of approval.

The Rules, cont.

- **TSCA also requires "Import Certification"** if you do import ski wax instead of make it here.
- **<u>Every time</u>** ski wax is imported, EPA requires the importer to certify that the products are 100% in compliance with TSCA. EPA and Customs review these records.
- By making this statement (under penalty of law), an importer is representing that they have checked every substance in each product that they are importing.

Wiley Rein

There is one additional requirement that applies to companies that import ski wax rather than make it here. Importers must certify under penalty of law that the ski waxes they import are in compliance with TSCA. This certification has to be made every time you import ski wax.

Later on in this presentation we will provide an example of how TSCA fines associated with multiple imports of a PFAS chemical that is not on the TSCA Inventory can exceed the penalties associated with making the same amount of the PFAS chemistry here in the US. This is not necessarily fair but it is a very real consequence of not staying on top of TSCA compliance if you are an importer.

TSCA Doesn't Only Apply to Toxic Substances - It Applies to Safe Ones, Too!

- **<u>TSCA applies to each component in ski wax products:</u>**
  - Hydrocarbon base (paraffin, microcrystalline or synthetic branched)
  - Rosins, solvents, fats
  - Electrostatic/dirt repellant
  - Speed additive (fluor or non-fluoro)
  - Colorant (waxes are color coded)
  - Fragrance
- Wax colors and fragrances, for example are mixtures themselves
  - Each one of the ingredients in a color or wax must be independently verified as compliant with TSCA.

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The name "Toxic" Substances Control Act is misleading, because TSCA applies to ALL chemicals whether they are safe or toxic.

The chemical supply chain can make TSCA verification difficult for companies down the supply chain. Many ingredients are not just single substances. Companies often purchase mixtures from other companies under a single trade name. Upstream suppliers may not want their customers to know everything that is in the raw material they are selling.

Let's think about this specifically in connection with what's in ski wax. It consists of a hydrocarbon base that might be a single chemical. However, some companies may add additional single ingredients like rosins, solvents, or fats. There is also an additive package on top of that which includes a repellent substance, speed additive like PFAS, a fragrance and a colorant. Many of these additives are most likely mixtures of individual chemicals.

Check All Ingredients…Even Mixtures…Even Non-Fluoros

- You need to know what is in all of the ski wax products you bring into the US or make here!
- You must check **<u>100% of ingredients</u>** in every product imported, manufactured, or distributed in the last 5 years to confirm that they are on the Inventory or exempt from TSCA… this includes mixture ingredients
- Ski waxes are mixtures of many substances. Ex., each wax color contains several ingredients and each one has to be identified.

Another misunderstanding that might be out there in the industry is that TSCA applies only to PFAS chemistry, so if your PFAS chemical is on the TSCA Inventory the wax can be shipped and represented as TSCA compliant. By now, I hope you are starting to understand that even though you may believe your fluorinated substances are on the TSCA list, you must review all your non-fluorinated products and ingredients as well, to include any liquid waxes, cleaners, non-fluorinated gliders, cross country kick waxes and klisters, every product you are selling into commerce that is not an article. The main point that needs to be understood by wax suppliers from this part of our presentation is that 100% of EVERY product must have be reviewed and properly documented.

What You Should Be Asking Your Suppliers.

- Identifying substances correctly and checking the list of EPA-approved ingredients requires expert advice on the accurate chemical nomenclature
- Ingredients are identified by:
  - Chemical Abstract Service Registry Numbers (CASRN)
  - Chemical Abstracts (CA) Index Names
  - Need High Degree of Specificity – General Names Won't Do!
- Proprietary Ingredients – NDAs or third party assistance
- Need documentation to protect yourself
  - SDSs, copies of import certifications, formulation list, Inventory check, exemption determinations, foreign supplier assurance letters.

Our experience in working with Swix is that the EU parent company did not immediately have all of the information we needed here to verify the TSCA compliance of all of the ingredients they purchase in Europe to make the wax that Swix USA imports. However, we were able to explain to them what we needed, and they were extremely helpful with communications up the supply chain to obtain the necessary information for us. Nevertheless, these communications and verification took a considerable amount of time. Also, while it is acceptable to work with EU suppliers, records of TSCA compliance should be kept in a central location in the United States and be sufficient to pass an EPA inspection. We will talk more about what is involved next.

Step-by-step: How to Verify TSCA Compliance

- **Review your Import History - 5-Year Look Back**
  - Ingredients in every product imported, distributed or manufactured in the US in the past 5 years need to be checked against EPA's list.
  - You are responsible for compliance during this time period **<u>even if you have stopped selling wax products.</u>**
- **100% ingredient check**
  - Must be identified correctly by Chemical Name and CASRN
  - Need 100% of the formulation - SDSs do not provide 100% of the formulation in many cases.
  - Communicate with Suppliers.
  - CASRNs used in the EU for REACH may not be the right ones to use for TSCA
  - Ingredients may be confidential so NDA's may be required
- **Document**
  - Ideally each chemical should be checked against the Inventory
  - Foreign supplier assurance letters - if they are wrong so are you.

TSCA ingredient reviews are complex and require special expertise in law, chemistry, and how EPA names chemicals on the TSCA Inventory list. Companies put themselves at a significant disadvantage if they respond to EPA information requests or take steps themselves to determine TSCA compliance without getting expert help. It is not EPA's job to teach you the rules. It is your responsibility to know the rules. If EPA contacts you and finds out you are not in compliance, they are required to follow through with an enforcement action.

Potential outcomes to prepare for before starting the verification process

- If a substance is **NOT** on the EPA's approved list, you must **STOP** importing, manufacturing, distributing.
- Knowingly doing so after that point exposes you to criminal enforcement by the federal government.
- If you stop voluntarily you are still liable for up to 5 years of prior non-compliance
- If you want to continue to sell, you need to tell EPA and get agency approval first.
  - EPA has a self-audit policy for voluntary disclosures that you might be able to use, but only if they have not already contacted you with a subpoena or an inspection notice.

We strongly recommend that you get advice about the potential for supply chain disruption and how to manage this before you start down the road of verifying the status of 100% of the ingredients you use or import. There are ways to minimize the impacts of a TSCA audit on downstream customers before the audit begins. These options may no longer be available once you know you have a problem. Once you know that a substance is not (READ SLIDE).

Now Tala and Tracy will provide more details on EPA's review of PFAS chemicals and what to expect from the EPA enforcement activity targeting ski wax products

What's At Stake – EPA Enforcement and Consequences of Non-Compliance

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Snowsports Industries America

Key Topics

- Who enforces?
- Who is potentially liable?
- How are violations discovered?
- EPA's enforcement mechanisms -- civil penalties; criminal liability and other actions
- Hypothetical import violation scenario
- Notable cases

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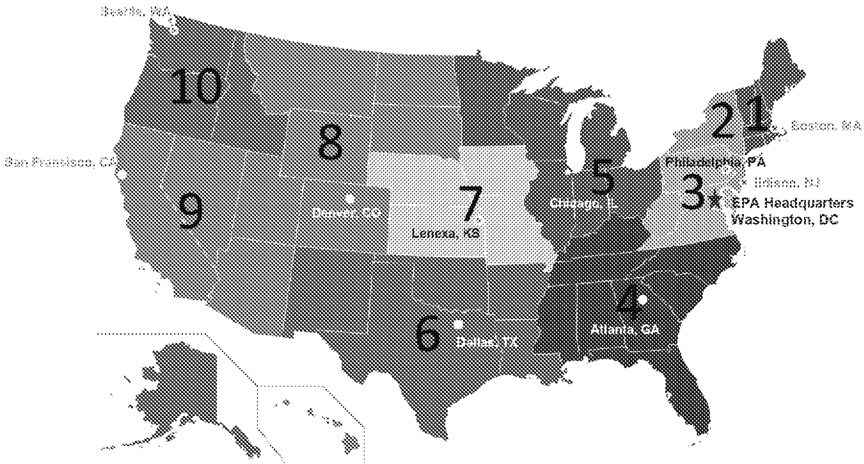
EPA Coordinates Enforcement Through 10 Regional Offices and EPA Headquarters



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You Need to Be Active In Being Compliant

- The EPA is an enforcement agency, not an educational agency. It's your responsibility to be 100% positive, that every substance, in every wax and product is compliant.
- You should know whether you are in compliance before importing and distributing your products.
- If you wait until EPA starts investigating, you will only make any potential violations worse

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As a wax supplier you SHOULD have in your belongings, files for each product, broken down by substance in your product, with certified CAS numbers for each substance. And if there are mixtures, each mixture must be broken down by substance and each substance must have a CAS number that is cross referenced to the EPA TSCA Substance Approved list. And it is not just for toxic substance like fluorocarbons, it's for all substance. (At this point you can tell them about the red dye story, 19 substance made up our red dye in the Swix CH8 product and Norway was buying this dye as a mixture from their supplier in Italy. Norway didn't know this, until now.

The main point that needs to be understood by the wax suppliers: It's important for the wax suppliers to know that in many cases, the parent company probably will not have all this information readily available so they need to obtain it, verify it (preferably with their legal counsel) and have in their possession. And they can not take the parents companies word for it, They must get verification from the suppliers (chemical companies) who are selling the chemicals to them, this is essential.

How are violations discovered?

- Inspections
- Subpoenas
  - EPA has broad authority under TSCA to issue subpoenas to collect information about products and the chemical substances contained in them.
  - Responding to a subpoena is MANDATORY
    - EPA is authorized to seek civil monetary penalties of up to **$39,873 <u>per day</u>** for failing or refusing to respond and submit information requested by a subpoena.
    - You may be fined or imprisoned for up to **5 years** for "knowingly or willingly" (1) falsifying, concealing or covering up factual information;

    OR (2) for making material false statements or representations to EPA.

How are violations discovered?

- Subpoenas – Special Declaration

  "I certify under penalty of law that I have personally examined and am familiar with the information submitted in this document (response to EPA subpoena) and all documents submitted herewith; that to the best of my knowledge and belief; the submitted information is true, accurate and complete; and that all documents submitted herewith are complete and authentic, unless otherwise indicated. I am aware that there are significant penalties for submitting false information, including the possibility of a fine or imprisonment."

- *DO NOT TRY TO REPLY TO A SUBPEONA WITHOUT LEGAL COUNSEL*

Who is liable for a violation?

- For chemical substances or products containing chemical substances in mixtures that are found not to be compliant with TSCA:
  - Importer
  - Processor/Manufacturer in the U.S.
- For retailers and distributors (if **not** importing) it depends on the facts of the situation.

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Importers

- Importer/distributors and companies that make ski wax in the US are responsible for compliance to the same degree as a US chemical manufacturer.
- For **<u>each shipment</u>** of chemical substances imported into the US, importers must certify that the products contained in the shipment are **<u>%100 TSCA compliant</u>**.
- Every time you import, you certify that your products are TSCA compliant!

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Import Certification Form

Toxic Substance Control Act (TSCA) Certification

Date:

Waybill or reference number:

Check only one

Positive Certification

☐ I certify that all chemical substances in this shipment comply with all applicable rules or orders under TSCA and that I am not offering a chemical substance for entry in violation of TSCA or any applicable rule or order thereunder.

or

Negative Certification

☐ I certify that all chemicals in this shipment are not subject to TSCA.

Company name:

Company address:

Certifier name:

Certifier title:

Certifier phone number:

Certifier email address:

Certifier signature:

Product description

1.
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8
9.
10.

If the certifier is unsure if their chemical substance is subject to TSCA compliance, contact the Environmental Protection Agency, TSCA Assistance Office at 1 202.554.1404 between 8:30 a.m. and 5:00 p.m.

Rev 1/17

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Import Certification Form

Toxic Substance Control Act (TSCA) Certification

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or

Negative Certification

☐ I certify that all chemicals in this shipment are not subject to TSCA.

Company name:

Check only one

Positive Certification

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or

Negative Certification

☐ I certify that all chemicals in this shipment are not subject to TSCA.

9.

10.

If the certifier is unsure if their chemical substance is subject to TSCA compliance, contact the Environmental Protection Agency, TSCA Assistance Office at 1 202.554.1404 between 8:30 a.m. and 5:00 p.m.

Rev 1/17

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EPA's Enforcement Options

- Civil Monetary Penalties
- Criminal Penalties – Fines and/or Imprisonment
- Seizure of Products
- Injunctions
- Other Sanctions by Customs and Border Patrol

Civil Monetary Penalties

- EPA can seek civil penalties for violations dating back 5 years.
- Maximum Civil Penalty: **<u>$39,873</u>** (per violation)
  - For certain types of violations – the penalty is "**per day**" of violation.
- Maximum Criminal Penalty: (for "knowing and willful" violations:
  - **<u>Up to $50,000 per violation (per day) or imprisonment for up to 1 year, or both.</u>**

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Civil Monetary Penalties

- EPA follows an "Enforcement Response Policy" to calculate civil penalties for violations.
- Complicated calculation based on a number of factors:
  - Type or Category of Violation
  - Circumstances – Level 1 or Level 2
  - Extent – Major, Significant or Minor
- EPA determines a "gravity based" penalty, which is then adjusted for inflation.

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Civil Monetary Penalties

- The "gravity based" penalty is multiplied by the number of violations
  - Violations can be "per day" or "one-day"
- Further adjustments can be made for:
  - Voluntary Disclosure – Decrease by 15% to 25%
  - Attitude – Increase or Decrease by 15%
  - History of Prior Violations – Increase depending on type of prior violation
  - Culpability – Decrease up to 25% depending on factual circumstances

Hypothetical Import Scenario

- For over 5 years, Ski Wax World has imported a product that includes an ingredient that is not in compliance with TSCA. To meet seasonal demand, Ski Wax World imports 15 shipments into the United States every year. All shipments come into the United States through the same Port of entry.

Penalty Calculation

EPA Section	Penalty Range ✖	Incidences Per Year =	Range Per Year
§5 Violation (Chemical Substance not on Inventory)	$39,873 – $7,778	15 shipments	$598,095 – $116,670
§13 Violation (Import certification is wrong)	$39,873 – $7,778	15 shipments	✚ $598,095 – $116,670
§5 Violation Penalty Range + §13 Violation Penalty Range			**Total Range Per Year $1,196,190 – $233,340**

Total Range Per Year
$1,196,190 – $233,340 ✖ **5 Years of Shipments** = **Total Penalty Range**
$5,980,950 – $1,166,700

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Notable Cases – Civil Penalties

- **Wilhemsen Ships Services, TSCA-HQ-2017-5006**
  - Penalty = **$1,300,000** (at settlement)
  - 135 imports from 2012 to 2016 of products with chemical substances not in compliance with TSCA
  - Section 8 Reporting violations
  - Total violations = approximately 289
  - Proposed penalty = approx. $7,000,000

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Notable Cases – Civil Penalties

- **Bethlehem Apparatus Company, TSCA-HQ-2012-5016**
  - Penalty = **$103,433** (at settlement)
  - 29 imports without proper certifications for individual shipments.
  - Export notification and reporting violations.
  - Proposed penalty unknown.

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The EPA Self-Disclosure/Audit Policy

- EPA has a voluntary self-disclosure policy that eliminates the potential for civil monetary penalties if certain conditions are met.
- You have **21 days** from the time of discovery to disclose the violation to EPA.
- ***Importantly, you must disclose a violation before getting a subpoena from EPA and you must promptly correct any violations in order to qualify.***

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Industry Misunderstanding: If I call up the EPA and tell them that I think I'm in violation, then I am relieved of my liability and cannot be at fault.
WR Message: To be relieved of a penalty or criminal action against you, you must complete a self-disclosure application. This will protect you from a subpoena but you may still be issued a fine. But very important, once you submit a self-disclosure application, you must then show proof to the EPA that you are or were not in compliance with TSCA and you have violated the law. EPA will decide to what extent to penalize you and you must cease to sell and distributor/importer/manufacturer wax and cleaners moving forward.

What's at Stake

- Concerns about PFAS not going away
- Many products that are active in commerce may not be in compliance.
- If EPA is investigating your business, the government is **obligated to fine you and make you stop selling non-compliant products.**
- **Do what is necessary to be compliant. The risks and costs of non-compliance are too high to ignore.**

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Questions?

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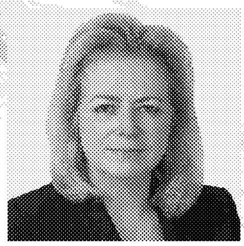

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TOXIC SUBSANCES CONTROL ACT (TSCA) & PFAS

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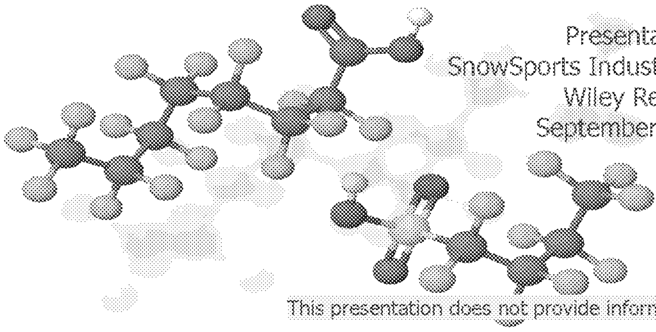
U.S. Environmental Protection Agency

Presentation to
SnowSports Industries of America &
Wiley Rein, LLC
September 26, 2019



This presentation does not provide information regarding compliance with TSCA.

EPA United States Environmental Protection Agency

TSCA: New Chemicals

- TSCA Section 2(b)(3):
  - Authority over chemical substances and mixtures should be exercised in such a manner *as not to impede unduly or create unnecessary economic barriers to technological innovation.*

  - While fulfilling the primary purpose of this Act to assure that such innovation and commerce in such chemical substances and mixtures *do not present an unreasonable risk of injury to health or the environment.*

Overview of New Chemicals Program

- Functions as a "gatekeeper" to help manage the potential risk to human health and the environment from chemicals new to the marketplace.

- Anyone who plans to manufacture (or import) a new chemical substance must provide EPA with notice - a Premanufacture Notice (PMN)

- EPA *must review* and evaluate new chemicals (or significant new uses of existing chemicals) and make an affirmative finding before those chemicals can enter the market

- Review must be completed within 90 days, with ability to extend 90 days

- If risks are identified, EPA *must* impose restrictions or prohibitions on the manufacturing, processing or use of the chemical to ensure the risks are mitigated

Exemptions from PMNs

- **Exemption Application <u>Not</u> Required for:**
  - R&D Chemicals
  - Exempted Polymers of Low Concern (only annual reporting)
- **Submission of Exemption Application Required:**
  - Low Volume (≤10,000 Kg/Yr) - 30 Day Review
  - Low Release/Exposure (LOREX) - 30 Day Review
  - Test Market Exemption (TME) - 45 Day Review
  - TSCA Experimental Release Application – 60 Day Review
  - Tier I and Tier 2 Biotechnology Exemptions
- For all exemption applications, EPA assesses whether the manufacture, processing, distribution in commerce, use or disposal of the substance will present an unreasonable risk to human health or the environment.

New Chemical Assessments

- New chemicals determinations are made using a risk-based approach, taking into account both hazard and exposure, under the substance's conditions of use (intended, known and reasonably foreseen).

- EPA assesses health and environmental hazards and exposures to:
  - multiple populations of humans: workers, consumers and general population, including susceptible subpopulations, e.g. different age groups of the general population)
  - the environment (e.g., primarily aquatic environment).

- Data required to be submitted with a new chemical (PMN) under TSCA is limited:
  - Details about how the chemical with be manufactured, processed and used
  - Only test data (e.g., fate tests, toxicity tests, etc.) that already exists; no new testing is required to be conducted for the submission.

- Therefore, EPA relies on predictive assessment methods, databases, and tools and models to evaluate chemicals throughout their lifecycle, i.e., manufacture, processing, distribution, use and disposal.

Types of Determinations under TSCA Section 5

Presents an Unreasonable Risk

- Section 5(f) order: Restriction/prohibition of manufacturing, processing, or distribution
- Section 6(a) Proposed Rule: Restriction/ prohibition of manufacturing, processing, distribution, or disposal

Not Likely to present an unreasonable risk

- Commercialization can commence after the determination is made
- Section 5(g) – Statement in the FR

Information is insufficient to permit a reasoned evaluation of the risk

- Section 5(e) – regulation pending more information
- Section 5(e) order

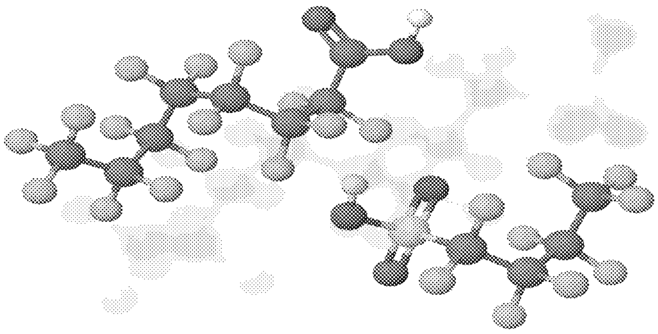
Insufficient information to permit a reasoned evaluation and **may present** unreasonable risk

- Section 5(e) – regulation pending more information
- Section 5(e) order

Significant New Use Rules (SNURs)

- A SNUR is a rule that identifies a potential new use of a chemical as a "significant new use."
- A manufacturer or processor intending to commence a significant new use must first submit to EPA a Significant New Use Notice (SNUN), and EPA must review and approve the use described in the SNUN before the company may commence manufacture or processing.
- TSCA authorizes EPA to propose or issue a SNUR for a chemical substance at any time, including during review of a section 5 notice for the chemical substance.

PFAS Activities under TSCA



What are PFAS?

- Per- and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals that have been in use since the 1940s.
- There are many PFAS chemicals, including the chemicals perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and GenX chemicals (HFPO dimer acid and its potassium salt).

What are PFAS?

- Due to their strong carbon-fluorine bonds, many PFAS can be very persistent in the environment with degradation periods of years, decades, or longer under natural conditions.

- Two of the most studied PFAS are Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS).

Where are PFAS found?

- PFAS are (or have been) found in a wide array of consumer products like cookware, food packaging, and stain and water repellants used in fabrics, carpets and outerwear.
- PFAS manufacturing and processing facilities, and airports and military installations that use firefighting foams which contain PFAS.

PFAS and TSCA

- 1,223 PFAS chemicals have been identified as being on the TSCA Inventory historically.

- There are 602 PFAS chemicals reported as active in commerce in the ten years prior to June 22, 2016.

PFAS and TSCA

TSCA TOOLS

- **Voluntary Agreements**
  - 2010/15 PFOA Stewardship Program
- **Regulatory**
  - Manage Alternatives - New Chemicals Program
  - Significant New Use Rules (SNURs)
  - Toxics Release Inventory (TRI)
  - TSCA Section 6 as Potential Tool for Risk Management

PFAS and TSCA

- **PFOS Phaseout**
  - EPA worked with industry to phase out production of PFOS and related chemicals between 2000 to 2002
- **2010/2015 PFOA Stewardship Program**
  - In 2006, EPA, in cooperation with eight major companies that manufactured and/or processed long-chain PFAS, launched the 2010/2015 PFOA Stewardship Program with the goal of eliminating long-chain PFAS from emissions and products by 2015
    - Arkema, Asahi Glass Company, BASF Corporation (formerly Ciba Specialty Chemicals Corporation), Clariant, Daikin, 3M/Dyneon, Chemours (formerly DuPont), and Solvay Solexis
  - All participating companies have met the PFOA Stewardship Program goals
  - Some companies that were not part of the PFOA Stewardship Program continue to produce/import and use PFOA and other long-chain PFAS that were phased out by others under the program

PFAS and TSCA

- **TSCA Activities for Existing PFAS Chemicals**
  - 2002: SNUR on 13 perfluoroalkyl sulfonate chemicals (67 FR 11008)
  - 2002: SNUR on 75 perfluoroalkyl sulfonate chemicals (67 FR 72854)
  - 2003: Enforceable Consent Agreement (ECA) Process (68 FR 18626) to develop data on use and production, exposure, toxicity, pharmacokinetics, and monitoring on long-chain PFAS
  - 2007: SNUR on 183 perfluoroalkyl sulfonate chemicals (72 FR 57222)
  - 2010: Premanufacture Notification Exemption for Polymers: Amendment of Polymer Exemption Rule to Exclude Certain Perfluorinated Polymers (75 FR 4295) revoking PFAS polymers from exemption under the polymer exemption rule
  - 2013: SNUR on long-chain perfluoroalkyl carboxylate chemical substances (LCPFAC) as part of carpets or carpet treatment products (78 FR 62443)
  - 2015: Proposed SNUR on LCPFAC and perfluoroalkyl sulfonate chemicals (80 FR 2885) to support the voluntary PFOA Stewardship Program phaseout of long-chain PFAS

EPA United States Environmental Protection Agency

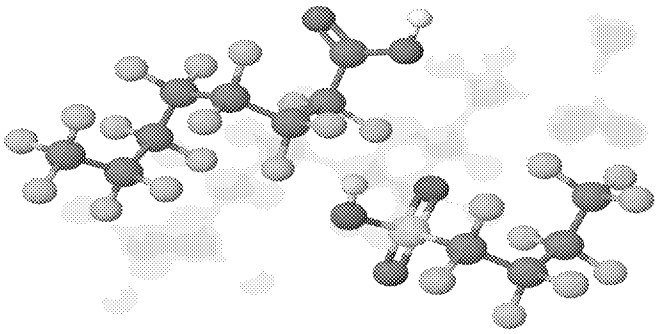
The significant new uses for perfluoroalkyl sulfonates in the 2002 and 2007 SNURs (CFR §721.9582):
Any manufacture or import for any use
Manufacture or import for the following specific uses is not considered as a significant new use subject to reporting (because these are ongoing uses and therefore not "new"):
Use as an anti-erosion additive in fire-resistant phosphate ester aviation hydraulic fluids
Use as a component of a photoresist substance, including a photo acid generator or surfactant, or as a component of an anti-reflective coating, used in a photomicrolithography process to produce semiconductors or similar components of electronic or other miniaturized devices
Use in coating for surface tension, static discharge, and adhesion control for analog and digital imaging films, papers, and printing plates, or as a surfactant in mixtures used to process imaging films
Use as an intermediate only to produce other chemical substances to be used solely for all of the uses listed above
Manufacture or import of tetraethylammonium perfluorooctanesulfonate (CAS No. 56773-42-3) for use as a fume/mist suppressant in metal finishing and plating baths (e.g., hard chrome plating; decorative chromium plating; chromic acid anodizing; nickel, cadmium, or lead plating; metal plating on plastics; and alkaline zinc plating)
Manufacture or import of a few perfluoroalkyl sulfonates for use as a component of an etchant, including a surfactant or fume suppressant, used in the plating process to produce electronic devices

The significant new uses for LCPFAC in the 2013 SNUR (CFR §721.10536):
Manufacture (including import) or processing for use as part of carpets or to treat carpets (e.g., for use in the carpet aftercare market)
Manufacture (including import) or processing of CAS No. 68412-68-0 and CAS No. 68412-69-1 for use as a surfactant in aftermarket carpet cleaning products is not be considered a significant new use subject to reporting

PFAS and TSCA

- In 2015, EPA published the proposed SNUR on LCPFAC to ensure that LCPFAC chemicals that have been phased out under the 2010/2015 PFOA Stewardship Program do not re-enter the marketplace without review
  - EPA intends to issue a supplemental SNUR for the import of certain LCPFAC chemical substances as part of categories of certain articles following changes to TSCA brought about by the Frank R. Lautenberg Chemical Safety for the 21st Century Act in June 2016 (RIN 2070-AJ99)

PFAS Background and Action Plan



United States
Environmental Protection
Agency

Action Plan Background

- EPA convened a two-day National Leadership Summit on PFAS in Washington, D.C.
- Following the Summit, the agency hosted a series of visits during the summer of 2018 in communities directly impacted by PFAS where EPA interacted with more than 1,000 people.
- The EPA's PFAS Action Plan was developed based on feedback from these events in addition to information received from approximately 120,000 comments submitted to the public docket.

Action Plan Purpose

- Provides EPA's first multi-media, multi-program, national research, management and risk communication plan to address a challenge like PFAS.
- Responds to the extensive public input the agency has received over the past year during the PFAS National Leadership Summit, multiple community engagements, and through the public docket.
- As a result of this unprecedented outreach, the Action Plan provides the necessary tools to assist states, tribes, and communities in addressing PFAS.

Highlighted Actions

- The EPA is committed to following the MCL rulemaking process as established by SDWA for water treatment and EPA will propose nationwide drinking water monitoring for PFAS under the next UCMR monitoring cycle.
- The EPA is initiating the regulatory development process for listing certain PFAS as hazardous substances.
- The EPA is rapidly expanding the scientific foundation for understanding and managing risk from PFAS.
- The EPA uses enforcement tools, when appropriate, to address PFAS exposure in the environment and assist states in enforcement activities.

Highlighted Actions

Toxics

- The EPA is considering the addition of PFAS chemicals to the Toxics Release Inventory
- EPA is issuing a supplemental proposal to guard against the unreviewed reintroduction and new use, through domestic production or import, of certain PFAS chemicals in the United States.

The EPA will provide updates on actions outlined in the plan on the Agency's website.

Thank you

Message

From: Ann Tveit [ann.tveit@basf.com]
Sent: 7/29/2020 9:47:34 PM
To: Stephanie Snyder [stephanie.snyder@covestro.com]; Stedeford, Todd [Stedeford.Todd@epa.gov]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Irwin, William [Irwin.William@epa.gov]; Rick_Becker@americanchemistry.com; Henry, Tala [Henry.Tala@epa.gov]; Owen Price [oprice@ara.com]; Salazar, Keith [Salazar.Keith@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]
Subject: RE: draft lung overload manuscript 27 July 2020.ver.4
Attachments: Draft manscript insoluble polymers and lung overload - 27 July 2020.ver.5.docx

Hi All,

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ann Tveit Ph.D., D.A.B.T.
Toxicology Manager

Phone: +1 973 245-5527, Mobile: Ex. 6 Personal Privacy (PP) - personal phone Email: ann.tveit@basf.com
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From: Stephanie Snyder <stephanie.snyder@covestro.com>
Sent: Wednesday, July 29, 2020 1:37 PM
To: Stedeford, Todd <Stedeford.Todd@epa.gov>; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael <hayes.mp@pg.com>; Ladics, Greg <gregory.s.ladics@dupont.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Ann Tveit <ann.tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Rick_Becker@americanchemistry.com; Henry, Tala <Henry.Tala@epa.gov>; Owen Price <oprice@ara.com>; Salazar, Keith <Salazar.Keith@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
Subject: RE: draft lung overload manuscript 27 July 2020.ver.4

Hi Todd,

The comments are contained in the attached version. **Ex. 5 Deliberative Process (DP)** **Ex. 5 Deliberative Process (DP)**

Thanks,
Stephanie

From: Stedeford, Todd [mailto:Stedeford.Todd@epa.gov]
Sent: Wednesday, July 29, 2020 5:58 AM
To: Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael; Ladics, Greg; Ogden, Julianne; Stephanie Snyder;

Tveit, Ann; Irwin, William; Rick_Becker@americanchemistry.com; Henry, Tala; Owen Price; Salazar, Keith; Jarabek, Annie
Subject: draft lung overload manuscript 27 July 2020.ver.4

All,

Here is the latest draft with comments/edits I received yesterday from Stephanie and from EPA. I kept the edits in track changes. Note, I also added some conclusions, which need review/editing. We can review this draft during our call today at 1 pm. If any of you have additional edits/comments, please keep them coming. I will continue to update as I receive them.

Thanks,

Todd

Polymer Lung Overload Category: The Application of New Approach Methodologies (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

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[j] SRC, North Syracuse, NY 13212, United States

KEYWORDS: Inhalation, Lung Overload, New Approach Methods, Particle Toxicity, Risk Assessment~~, (Word Style "BG_Keywords"). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval~~.

ABSTRACT

Poorly soluble and non-reactive high-molecular weight (HMW) polymers (≥10,000 Daltons) represent a generic category of substances that are extensively used in industrial and consumer applications (*e.g.*, plastics). Under the amended Toxic Substances Control Act (TSCA), HMW polymers may qualify for an exemption from the pre-notification requirements that exist for polymeric, new chemical substances. However, for HMW polymers that do not meet the exemption criteria and are produced in a respirable form (*e.g.*, powders), the U.S. Environmental Protection Agency (EPA) will evaluate hazards and risks of these substances for lung overload. In the present evaluation, a systematic review of the literature was performed to identify studies that would aid with defining key properties for determining whether respirable HMW polymers may present an unreasonable risk to human health. These properties included: respirability, reactivity, and solubility and were used for defining the inclusion/exclusion criteria for a

chemical category on HMW polymers. Available inhalation toxicity studies for HMW polymers were evaluated and dosimetric adjustments used to derive human equivalent concentrations for ~~several~~ a toxicological analogues~~s~~ that ~~can~~ may be used in risk assessments on these substances. Finally, a tiered-testing strategy that maximizes the use of non-vertebrate testing (*i.e.*, NAMs) was developed that may be used to evaluate newer chemistries to determine whether they fit within the chemical category of HMW polymers that may present a lung overload hazard or for refining risk estimates for such chemical substances.

INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law on June 22nd, 2016, thereby amending the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law for regulating new and existing chemical substances. The amendments to TSCA placed new requirements on the U.S. Environmental Protection Agency (hereinafter "EPA" or the "Agency") to reduce and replace vertebrate animals in testing of chemical substances, to the extent practicable and scientifically justified, and requires EPA to make one of the following five determinations for new chemical substances, based on unreasonable risk, sufficiency of information, and exposure:

1. The new chemical substance or significant new use presents an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(A));
2. The available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the new chemical substance or significant new use (TSCA §5(a)(3)(B)(i));

3. In the absence of sufficient information, the new chemical substance or significant new use may present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(B)(ii)(I));
4. The new chemical substance is or will be produced in substantial quantities and either enters or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the new chemical substance (TSCA §5(a)(3)(B)(ii)(II)); or
5. The new chemical substance or significant new use is not likely to present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(C)).

For findings of unreasonable risk, EPA is required to take risk management actions (*e.g.*, consent orders with testing requirements, restrictions on manufacturing, processing, use, disposal, *etc.*) to address unreasonable risks before a company may commence manufacture or processing of the new chemical substance.

EPA reviews all data submitted with a new chemical substance notification; however, unlike laws with prescribed, “up-front” testing requirements (*e.g.*, Federal Insecticide, Fungicide, and Rodenticide Act), the data requirements for new chemical substance notifications are limited to health or environmental effects in the possession or control of the entity submitting the new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>31</RecNum><DisplayText>[1]</DisplayText><record><rec-number>31</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595768685">31</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 720.50 - Submission of test data and other data concerning the health and environmental effects of a substance</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><dates><year>2020</year></dates><pub-location>U.S.</pub-location><urls><related-urls><url>https://www.law.cornell.edu/cfr/text/40/720.50</url></related-urls></urls></record></Cite></EndNote>].

EPA has historically used various approaches to evaluate the potential hazards of new chemical substances including ~~the use of~~ computational toxicology models and ~~analogue and~~ category approaches to "read-across" from existing data to new chemical substances for various requisite extrapolations. EPA's TSCA New Chemicals Program (NCP) developed 56 chemical categories (hereinafter the "NCP Chemical Categories") based on specific ~~chemical~~ definitions and boundaries that summarize the hazard concerns (*e.g.*, human health or environmental toxicity) and recommend testing ~~that may be conducted~~ prior to submitting a new chemical substance notification [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>T

SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

Although the NCP Chemical Categories document provides transparency to the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physical properties~~to the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physical properties~~, the NCP Chemical Categories were developed prior to the ~~enactment of the~~ amendments to TSCA, and therefore, do not reflect vertebrate testing reduction goals. For example, the testing strategy in the NCP Chemical Categories document for respirable, poorly soluble particulates[1] includes ~~vertebrate animal testing, such as~~ a 90-day subchronic inhalation toxicity study in rats with a 60-day recovery period [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key

[1] EPA identified particles as “respirable” to humans “if there are any particles $\leq$10 μ[m] in diameter in the material being handled by workers” and included “poorly soluble” compounds citing ILSI (2000) [56].

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Further, the NCP Chemical Categories cover ~~the~~ defined boundaries ~~defined therein~~and therefore may not ~~reflect development of~~include alternative chemistries that are intended to replace a chemical in the ~~do not fit within the~~ current NCP Chemical Categories~~, even for chemicals that the alternative chemistries are intended to replace~~ (*e.g.*, the use of polymeric alternatives to replace monomeric forms of existing chemical substances).

Based on the Agency's experience gained by reviewing over 12,000 polymers, EPA has ~~also~~ developed exemption criteria for specific types of polymeric substances, based on its findings that they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption"~~, for specific types of polymeric substances~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]. New chemical substances meeting these criteria are exempt from the new chemical substance notification requirements, although there are still ~~some requirements, including~~ annual reporting and recordkeeping requirements [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

EPA~~'s polymer exemption~~ established three polymer exemption types, designated as E1, E2, and E3. The general criteria for new ~~chemical~~ polymer substances meeting these exemption types ~~for polymers~~ are shown in [REF _Ref46665925 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. EPA's exemption criteria for new chemical substances meeting the regulatory definition of a polymer.[a,b]

Exemption Type	*Number-average molecular weight (NAMW)*	*Oligomeric Material Criteria*	*Functional Groups (FGs) and Functional Group Equivalent Weight (FGEW) Content*
E1	1,000 ≤ NAMW < 10,000	< 10 wt% below 500 Daltons < 25 wt% below	Low concern FGs:[c] no limit Moderate-concern FGs: FGEW ≥ 1,000 Moderate-concern FGs + High concern FGs: $FGEW_{combined}$ ≥ 5,000 High-concern FGs: FGEW ≥ 5,000

		1,000 Daltons	
E2	NAMW ≥ 10,000	< 2 wt% below 500 Daltons < 5 wt% below 1,000 Daltons	No FG restrictions
E3	No limit	No limit	Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[a] See 40 CFR § 723.250(b) Polymers. “Polymer means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition, sequence means that the monomer units under consideration are covalently bound to one another and form a continuous string within the molecule, uninterrupted by units other than monomer units.” [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[b] The following exclusions apply: Cationic polymers, see 40 CFR § 723.250(d)(1) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Elemental limitations, see 40 CFR § 723.250(d)(2) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers which degrade, decompose, or depolymerize, see 40 CFR § 723.250(d)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers manufactured or imported from monomers and reactants not on the TSCA Chemical Substance Inventory, see 40 CFR § 723.250(d)(4) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Water absorbing polymers with NAMW $\geq$ 10,000 Daltons, see 40 CFR § 723.250(d)(5) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 -

Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; and Polymers which contain certain perfluoroalkyl moieties consisting of a CF3- or longer chain length, see 40 CFR § 723.250(d)(6) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

[c] "These groups are so categorized because they generally lack reactivity in biological settings"; see EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]; for discussion, see: EPA (1995) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type

name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>].

~~As noted, for new chemical substances that meet the polymer exemption criteria, EPA has determined they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption"~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[3]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]~~; however, t~~There are instances, however, where exempt polymers, as well as non-exempt polymeric substances, may be manufactured, processed, used, *etc*., in a manner that may create hazards, which are not intrinsic to the polymer *per se*, but rather ~~are based~~ on the form of the polymer (*e.g.*, respirable). For example, high-molecular weight (HMW) polymers (*i.e.*, NAMW ≥ 10,000 Daltons) that meet the E2 criteria and are manufactured or used as particles with sizes in the respirable range (*i.e.*, ≤ 10 μm) represent a ~~general~~ class of chemical substances (hereinafter referred to as "HMW polymers") that may cause an~~potential~~ inhalation ~~toxicity~~ hazard (*i.e.*, lung overload) *via* the mode(s) of action (*i.e.*, impairment of alveolar-macrophage mediated clearance), as identified in rat inhalation studies, to chemical substances ~~present~~ in the respirable, poorly soluble particulates ~~in the~~ NCP Chemical Categor~~ies document for respirable, poorly soluble particulates~~y. ~~However,~~

~~the chemical substances that are provided as~~ The analogues for the respirable, poorly soluble particulates ~~within the boundaries for the~~ NCP Chemical Category ~~on respirable, poorly soluble particulates~~ are ~~limited to~~ discrete inorganic substances, including oxides of various metals (*e.g.*, titanium dioxide) or nonmetals (*e.g.*, carbon black). In contrast, HMW polymers consist of the polymeric substance, as well as varying weight fractions of oligomeric material (*e.g.*, < 5 wt% below 1,000 Daltons for ~~those~~ polymers meeting the E2 criteria).

The purpose of the present evaluation was to perform a systematic review of the literature to identify available information that would support: (1) establishing physicochemical boundaries for a chemical category on HMW polymers; (2) determining whether specific chemical substances could be used as representative toxicological analogues with points of departure for the members of this category; and (3) establishing a proposed tiered-testing strategy for evaluating new chemical substances that meet the chemical boundaries for this category. ~~An additional aim was to introduce~~ In addition, new approach methodologies (NAMs) were introduced as part of the tiered-testing strategy ~~to~~ that meet the statutory mandate under TSCA to reduce or replace the use of vertebrate animals in the testing of chemical substances.

MATERIALS AND METHODS

Systematic Literature Review

An initial literature search was conducted in November 2016, and a supplemental literature search was conducted in April 2018. The details of these reviews, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcomes (PECO) criteria used for reviewing results for relevance are provided in the Supporting Information file at

"Section 1 Systematic Literature Review". The objective of these reviews was to obtain studies that evaluated potential "lung overload" toxicity, *i.e.*, respiratory tract toxicity of HMW polymers in exposed humans, investigated lower respiratory tract (*i.e.*, the tracheobronchial and alveolar regions) effects in laboratory animals and identified points of departure, or informed the mode of action for these agents at a cellular level (*i.e.*, *in vitro* studies). In the context of this evaluation, "lung overload" refers to the "type of retained lung burden seen with excessively high exposures [in rodents] that lead to impairment of AM [alveolar macrophage]-mediated particle clearance" [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2000</Year><RecNum>37</RecNum><DisplayText>[6]</DisplayText><record><rec-number>37</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595773878">37</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author></authors></contributors><auth-address>Chemical Industry Institute of Toxicology, 6 Davis Drive, PO Box 12137, Research Triangle Park, NC 27709, USA. fmiller@ciit.org</auth-address><titles><title>Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>19-57</pages><volume>12</volume><number>1-2</number><edition>2000/03/15</edition><keywords><keyword>Air Pollutants/*adverse effects/pharmacokinetics</keyword><keyword>Air Pollutants, Occupational/*adverse effects/pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Animals, Laboratory</keyword><keyword>Body Burden</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Humans</keyword><keyword>Lung/*drug effects/metabolism</keyword><keyword>Pneumoconiosis/*etiology/metabolism</keyword><keyword>Risk Assessment</keyword><keyword>Species Specificity</keyword></keywords><dates><year>2000</year><pub-dates><date>Jan-Feb</date></pub-dates></dates><isbn>0895-8378 (Print)
0895-8378</isbn><accession-num>10715617</accession-num><urls></urls><electronic-resource-num>10.1080/089583700196536</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Since “overload” is defined differently in experimental animals versus humans [ADDIN EN.CITE ADDIN EN.CITE.DATA], the literature searches used search strings that were intended to be overly inclusive to identify studies that evaluated “overload” in experimental animals and humans. A secondary objective was to identify potential NAMs that may be incorporated into a tiered-testing strategy that minimizes the use of vertebrate animals.

Risk Assessment Approaches Under TSCA

EPA generally uses ~~the~~ a margin of exposure (MOE) approach for quantifying potential non-cancer risks in risk assessments ~~performed~~ on new chemical substances ~~under TSCA~~. The MOE ~~approach~~ is calculated based on a point(s) of departure (POD) divided by ~~a~~ the human exposure estimate(s). The POD is ~~typically identified~~developed from an effect level ~~from a study(ies) in experimental animals~~ (*e.g.*, no-observed-adverse-effect concentration [NOAEC], lowest-observed-adverse-effect concentration [LOAEC], or benchmark dose [BMD]) typically identified from animal studies. An ~~duration~~ adjustment is applied to the POD to account for the exposure conditions under evaluation (*e.g.*, workers = 8 hours/day, 5 days/week) versus the exposure conditions ~~employed~~ in the experimental study (*e.g.*, 6 hours/day, 5 days/week). The human exposure estimate is typically generated ~~for new chemical substances~~ using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as acute potential dose rates (PDRs) in mg/day or lifetime average daily doses (LADDs) in mg/kg-bw/day. Given that most new chemical substances ~~will~~ usually do not have occupational exposure monitoring data, ~~except for possible monitoring data on analogues,~~ the PDR is ~~typically~~ used as an initial conservative exposure estimate when calculating the MOE. For chemical substances ~~used~~ in a powder or particulate form, the ~~general~~ default PDR values for respirable ~~or~~ and total particulates are 50 mg/day (*i.e.*, 5 mg/m^3) ~~or~~ and 150 mg/day (*i.e.*, 15 mg/m^3), respectively [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>44</RecNum><DisplayText>[12]</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595776956">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>399</pages><dates><year>2013</year></dates><urls></urls></reco

rd></Cite></EndNote>]. However, for chronic effects like lung overload, the LADD represents the more appropriate exposure metric for quantifying potential risks [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>45</RecNum><DisplayText>[13]</DisplayText><record><rec-number>45</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595778575">45</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Interpretive Assistance Document for Assessment of Discrete Organic Chemicals, Sustainable Futures Summary Assessment</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>20, https://www.epa.gov/sites/production/files/2015-05/documents/05-iad_discretes_june2013.pdf</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. A summary of the default values used ~~for~~ in calculating PDRs and LADDs for new chemical substances in powder or particulate form is provided in [REF _Ref46666189 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. Default values used for calculating the PDR and LADD.

Description	Equation	Parameter	Defaults	Units
PDR (mg/day)	$Cm \times b \times h$	Mass concentration of chemical in air (Cm)	5	mg/m^3

		Volumetric inhalation rate (b) $(0 < b \leq 7.9)$	1.25	m^3/hr
		Exposure duration (h) $(0 \leq h \leq 24)$	8	hrs/day
LADD (mg/kg-bw/day)	(I × ED × EY) / (BW × ATc × 365 days/yr)	Inhalation PDR (I)	50	mg/day
		Days exposed per year (ED) $(0 \leq$ ED (integer) $\leq 365)$	250	days/site-yr
		Years of occupational exposure (EY) $(0 \leq \text{EY})$	40	years
		Body weight (BW) $(0 \leq \text{ATc})$	80	kg
		Averaging time over a lifetime (chronic) $(0 \leq \text{ATc})$	70	years

For each of the MOEs calculated ~~herein~~in this article, both the PDR and LADD have been provided ~~are provided~~ for comparison. The resulting MOE is compared to a benchmark MOE for characterizing potential risks. If the MOE is lower than the benchmark MOE, potential risks are indicated under TSCA, whereas if the MOE is higher than the benchmark MOE, the ~~risks are not considered a concern under TSCA~~chemical substance is considered as not posing a potential risk.

Benchmark MOE Derivation

The benchmark MOE ~~is derived to~~ accounts for both uncertainty and variability. In the context of this article, these terms have the same meaning as defined by EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><Dis

playText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] and are based on the following considerations: intraspecies (a.k.a., intrahuman) variability (*i.e.*, human-to-human variability or UF_H), interspecies variability (*i.e.*, animal-to-human extrapolation uncertainty or UF_A), and LOAEC-to-NOAEC uncertainty (*i.e.*, uncertainty with extrapolating from a Lowest Observed Adverse Effect Concentration [LOAEC] to a No Observed Adverse Effect Concentration [NOAEC] or UF_L). The default values used for calculating the benchmark MOE are 10 for each of the composite uncertainty factors (*i.e.*, $UF_H \times UF_A \times UF_L = 1000$). EPA has developed guidance ~~focused on improving~~to improve the science underlying the animal-to-human uncertainty factor, which provides generalized procedures for deriving dosimetric adjustment factors (DAF) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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Review of the Reference Dose and Reference Concentration Processes</title><secondary-
title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC
20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S.
Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192,
https://www.epa.gov/sites/production/files/2014-12/documents/rfd-
final.pdf</pages><volume>EPA/630/P-
02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><
Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-
number>47</rec-number><foreign-keys><key app="EN" db-
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Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation
Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental
Protection Agency, Research Triangle Park, North Carolina</secondary-
title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental
Protection Agency, Research Triangle Park, North Carolina</full-
title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-
11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-
90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot
e>]. Application of DAFs to the animal airborne exposure values yields estimates of the

concentration ~~that would result in the same concentration to~~in humans, ~~that is,~~ the Human Equivalent Concentration (HEC). For studies ~~reporting~~ with only a LOAEC, EPA recommends benchmark dose modeling be performed~~, if the experimental data are amenable,~~ to identify a BMDL ~~, and thereby~~to reduce the LOAEL-to-NOAEL UF value to 1. Each of these adjustments is discussed below, along with their potential applicability to the available studies that evaluated lung overload from HMW polymers.

Regional Dose Dosimetry Ratio (RDDR)

EPA may apply DAFs to PODs ~~identified~~ from experimental animal studies based on the methods described in ~~its~~ EPA's 1994 guidance document ~~titled~~ "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-

11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-
90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot
e>]. ~~When applied~~In this method, the default DAF accounts for the toxicokinetic component of the UF_A and is reduced from approximately 3 (*i.e.*, $10^{0.5}$) to 1, ~~since~~ the POD is dosimetrically adjusted to a POD_{HEC} ~~, whereas~~and the ~~remaining~~ UF_A value of approximately 3 accounts for the toxicodynamic component of the UF_A. EPA's 1994 guidance document recommends the use of ~~Dosimetry~~ dosimetry or physiologically-based pharmacokinetic models ~~are preferred to the~~over default models when they are available [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><Dis
playText>[15]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
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Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation
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Protection Agency, Research Triangle Park, North Carolina</full-
title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-
11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-
90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot
e>].

To derive a DAF for particle exposures, EPA developed a software program for calculating the regional deposited dose ratio (RDDR), ~~that is,~~ the DAF for particles. The RDDR is an empirical model of deposition, ~~that is~~ applicable to particles in the size range of 0.5-30 μm and calculates an RDDR ~~value~~ as the DAF for insoluble particles using the following ratios:

$$RDDR = \frac{V_{E,animal}}{V_{E,human}} \times \frac{F_{r,animal}}{F_{r,human}} \times \frac{NF_{human}}{NF_{animal}}$$

These ratios incorporate animal to human adjustments for the following parameters: minute volume (V_E; mL/min), depositional fraction (Fr) ~~of the particulate~~ in the different regions of respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a normalizing factor (NF) for the region of interest, such as respiratory tract surface area~~, for the region of interest~~. The RDDR ~~user~~ inputs include mass median aerodynamic diameter (MMAD), geometric standard deviation (σ) ~~for the particle of interest~~, and the average bodyweight of the animal ~~used in the study~~ from which default V_E and surface areas of the respiratory tract regions ~~for the animal~~ are calculated. The RDDR may be applied to the ~~duration~~ duration-adjusted POD; however, risk assessments performed under TSCA apply the RDDR to the POD obtained ~~under~~ in the laboratory animal regimen~~. Thereafter,~~ and the duration adjustment is applied when quantifying the MOE for the population of interest. The RDDR software (version 2.3) was run with the assistance of DOSBox, an open-source and free DOS-emulator [ADDIN EN.CITE <EndNote><Cite><Author>DOSBox</Author><Year>2019</Year><RecNum>48</RecNum><DisplayText>[16]</DisplayText><record><rec-number>48</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789343">48</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>DOSBox</author></authors></contributors><titles><title>DOSBox "Way more FPA than Counterstrike !"</title></titles><pages>https://www.dosbox.com/</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>].

Multiple-Path Particle Dosimetry (MPPD)

Inhaled dose is dictated by inhalability and deposition mechanisms that differ in relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation tidal volume and breathing rate; and as well interact with key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the integrated processes of inhalability, deposition, and clearance.

The Multiple-Path Particle Dosimetry (MPPD) model (version 3.04) developed by Anjilvel and Asgharian (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Anjilvel</Author><Year>1995</Year><RecNum>73</RecNum><DisplayText>[17]</DisplayText><record><rec-number>73</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839173">73</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anjilvel, S.</author><author>Asgharian, B.</author></authors></contributors><auth-address>Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.</auth-address><titles><title>A multiple-path model of particle deposition in the rat lung</title><secondary-title>Fundam Appl Toxicol</secondary-title><alt-title>Fundamental and applied toxicology : official journal of the Society of Toxicology</alt-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>41-50</pages><volume>28</volume><number>1</number><edition>1995/11/01</edition><keywords><keyword>Airway Resistance/physiology</keyword><keyword>Animals</keyword><keyword>Bronchi/anatomy & histology/physiology</keyword><keyword>Lung/*anatomy & histology/physiology</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Respiratory Function Tests</keyword><keyword>Respiratory Mechanics/physiology</keyword><keyword>Tidal Volume/physiology</keyword><keyword>Trachea/anatomy & histology/physiology</keyword></keywords><dates><year>1995</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590</isbn><accession-num>8566482</accession-num><urls></urls><electronic-resource-num>10.1006/faat.1995.1144</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and updated by Miller *et al.* (2016) [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2016</Year><RecNum>70</RecNum><DisplayText>[18]</DisplayText><record><rec-number>70</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838679">70</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author><author>Asgharian, B.</author><author>Schroeter, J.D.</author><author>Price, O.</author></authors></contributors><titles><title>Improvements and additions to the Multiple Path Particle Dosimetry model</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>14-26</pages><volume>99</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] is a mechanistic, multipath model that was modified and used to predict deposition, clearance, and lung burden over the course of a long-term exposure , as described by Ladics *et al*. (2020) [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[19]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In

preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. As with the RDDR outputs, the MPPD outputs provide values that may be used to calculate a POD_{HEC}; however, unlike the RDDR model, MPPD provides outputs that may be used to characterize acute exposures *via* deposition and subchronic/chronic exposures *via* retained dose.

The MPPD model (version 3.04) uses default translocation rates in the alveolar interstitium that were recommended by the International Commission on Radiological Protection (ICRP) in their 1994 human respiratory tract model [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title> Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-

Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. These rates are considered representative of insoluble particles. More recently, the ICRP model and clearance rates have been updated based on improved lung burden data [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Refinements may be imparted by chemical-specific dissolution data and exploration of these new model values. Hygroscopic growth is currently not addressed in either the MPPD or ICRP models; and is not likely to be relevant to this category of inhaled polymers. In rats, MPPD implements a two-compartment pulmonary clearance model where the alveolar clearance rate decreases as alveolar retained mass increases. MPPD predicts the alveolar clearance rate based on an empirical model fit to titanium dioxide retained mass data from 13-week rat exposures. In humans, MPPD implements the ICRP clearance model localized for individual airways in the pulmonary region. Clearance rates in the ICRP human clearance model are constant and do not vary with alveolar retained mass. Therefore, depression of clearance rates associated with lung overload is incorporated in the MPPD rat model, but not the MPPD human model. Additional uncertainty in the predictions is imparted from the use of lung geometry models for different rat species than used in the experiment, but nonetheless will be shown to fit experimental data well.

Benchmark Dose Modeling

EPA's benchmark dose modeling (BMD) software is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach~~, as discussed in EPA (2012)~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not ~~identified~~ available in a study, EPA typically applies a UF_L of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the UF_L may be reduced from 10 to 1. ~~, because t~~The statistical lower confidence limit on the concentration at the BMD (*i.e.*, the BMDL) is a dose level corresponding to specific response levels near the low end of the observable range ~~of the data and~~that incorporates and conveys more information than the NOAEC or the LOAEC [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, ~~and~~ model fit ~~was~~ evaluated using the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit ~~as displayed graphically~~. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[22]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

RESULTS AND DISCUSSION

Literature Search and Screening Results

The initial literature search identified 257 articles on PubMed. Following title and abstract screening, 28 articles were selected for full text review, and 23 articles were identified using additional search strategies (*e.g.*, tree searching). Of the 51 articles identified for full text review, only 24 articles contained relevant information that satisfied the PECO criteria for lung overload from HMW polymers. In the supplemental literature search, 1218 articles were identified on PubMed and Embase (combined). Title and abstract screening resulted in 46 potentially relevant articles for full text screening. Of these, 13 were identified as potentially relevant for review; seven of the13 articles were also identified in the initial literature search. Complete details on the systematic review are provided in the Supporting Information file at “Section 1 Systematic Literature Review”.

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries, to develop the health effects summaries in the section on Hazard Identification, and to identify NAMs to include in the section on Tiered-Testing Strategies.

Category Boundaries

The ~~category~~ boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA’s polymer exemption at 40 CFR § 723.250(d) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[4]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA’s polymer exclusion criteria, is discussed ~~further~~ below.

It should be noted, although ~~that even if~~ a HMW polymer satisfies the ~~category~~ boundary criteria for the category, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

Respirable particles are those chemical substances with a particle size of less than or equal to 10 μm. The cutoff of 10 μm, as defined by EPA in its “Air Quality Criteria for Particulate Matter”, represents “particles collected by a sampler with an upper 50% cut point of 10 μm D_a [aerodynamic diameter] and a specific, fairly sharp, penetration curve” [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. However, depending on the sampling method and size fraction collected, the sample may contain particles between 10 and 30 µm diameter that are excluded from the 10 µm D_a fraction [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[23]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. In comparison, occupational health organizations rely on unified size fraction definitions based on the upper size ~~cuts~~ of particles and entry into the different regions of the respiratory tract. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) considers 10 µm D_a particles as an upper limit for particles ~~with this size~~ entering the alveolar region [ADDIN EN.CITE <EndNote><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><DisplayText>[24]</DisplayText><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Further, consideration must ~~also~~ be given to the particle settling ~~that may occurr~~ate. ~~For example,~~ ~~i~~In still air, 10 μm spherical particles with a density of 1 g/cm^3 can remain airborne for approximately 8 minutes [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-

title></periodical><pages>40,

https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]~~. However~~, and as particle size decreases, the airborne settling time increases (*e.g.*, approximately 1.5 hours for 3 µm particles to settle in still air) [ADDIN EN.CITE

<EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[24, 25]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40,

https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-

title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Therefore, solids with even a small fraction of respirable particles may produce prolonged and elevated airborne levels of respirable particles in the workplace. ~~Though~~ Although occupational monitoring data provide ~~the most direct~~ assurance that airborne levels of respirable particles do not exceed relevant exposure limits, particle size distribution data are typically the only metric available for estimating potential respirability for new chemical substances. Given this limitation and ~~the reality~~ that ~~nearly all~~ solid particulate materials may contain some percentage of respirable particles, a practical screening cutoff is warranted for category inclusion/exclusion. For the purposes of this category, we propose that HMW polymers are considered respirable if they are manufactured, processed, used, *etc*., in a manner that generates the new chemical substance with a particle or aerosol size of less than or equal to 10 µm or if respirable particles may be unintentionally generated during the life cycle of the material (*e.g.*, impaction and friction during transport). Under the latter scenarios, ~~a practical cutoff of ≥~~particles that are greater than or equal to 1% respirable particles by weight (wt%) based on particle size distribution data for the material is the practical ~~as the~~ cutoff for assessing respirable particles and ~~this percentage would be based on particle size distribution data for the material. The practical cutoff of ≥ 1 wt%~~ is the same cutoff EPA applies to the nonreportable content of nanoscale materials [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>54</RecNum><DisplayText>[26]</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791830">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ~~This~~ The same cutoff would apply to the particle/droplet size distribution ~~in the case of~~for aerosols of a solid or liquid chemical substance and would be determined based on droplet size data for the material and/or liquid application method (*e.g.*, spray, aerosol, mist).

EPA's Functional Group (FG) and Functional Group Equivalent Weight (FGEW) criteria for E1 polymers provide a starting point for evaluating the potential reactivity and/or cytotoxicity of HMW polymers. Therefore, we propose using these criteria as an initial screen for determining whether a HMW polymer is considered non-reactive and included or reactive and ~~included or~~ excluded from the category~~, respectively~~. As shown in [REF _Ref46665925 \h * MERGEFORMAT], the E1 polymer exemption criteria include low-concern, moderate-concern, or high-concern FGs. ~~A summary of r~~Representative FGs meeting each of these hazard concern levels is shown in [REF _Ref46674358 \h * MERGEFORMAT].

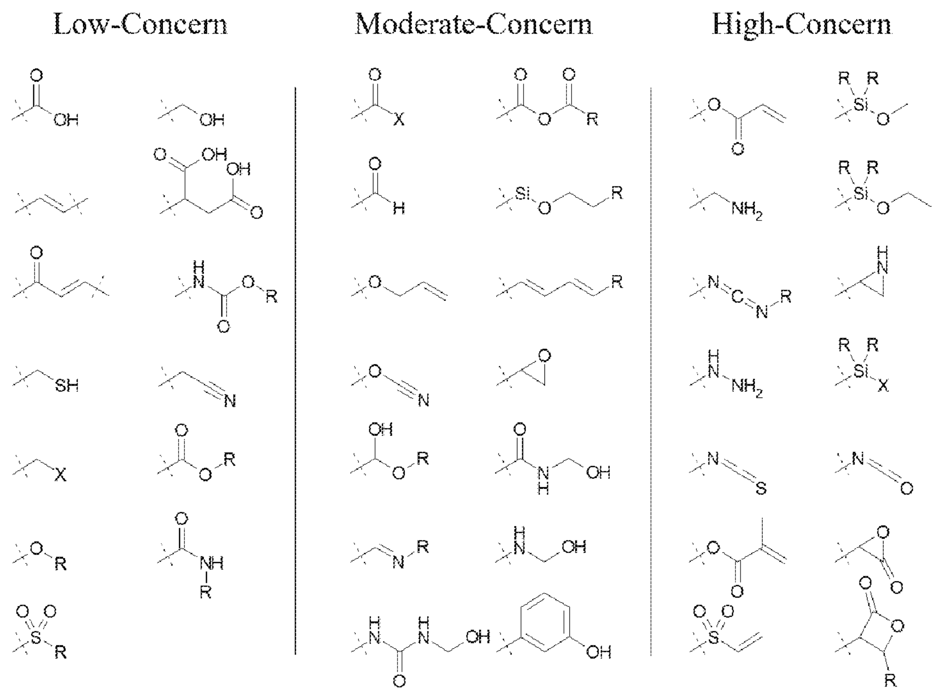


Figure [SEQ Figure * ARABIC]. FG hazard concern levels for polymeric substances meeting EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern) for the HMW polymer category. The following cutoffs are proposed as the category boundaries for establishing that a HMW polymer is non-reactive: low-concern FGs (no limit), moderate-concern FGs (FGEW ≥ 1,000), or high-concern FGs (FGEW ≥ 5,000). "R" represents an undefined structure; "X" represents a halide. See: EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[5]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] for further details.

A ~~generally recognized~~ property of respirable, low reactive (*i.e.*, low toxicity) particles that ~~can~~ may cause lung overload is the poorly soluble nature of these compounds. EPA has published general water solubility classifications, which include: negligible solubility (*i.e.*, < 0.1 mg/L), slight solubility (*i.e.*, > 0.1 - 100 mg/L), moderate solubility (*i.e.*, > 100 - 1,000 mg/L), soluble (> 1,000 - 10,000 mg/L), and very soluble (> 10,000 mg/L) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>56</RecNum><DisplayText>[27]</DisplayText><record><rec-number>56</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792442">56</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Section 5. Estimating Physical/Chemical and Environmental Fate Properties with EPI SuiteTM,

Sustainable Futures/P2 Framework Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>22, https://www.epa.gov/sites/production/files/2015-05/documents/05.pdf</pages><volume>EPA-748-B12-001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. These values were not established for evaluating the solubility of particles for lung overload; however, they may be used as conservative cutoffs for extractability, per OECD TG 120 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2000</Year><RecNum>55</RecNum><DisplayText>[28]</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792078">55</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Solution/Extraction Behaviour of Polymers in Water</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>4, https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-chemical-properties_20745753</pages><volume>120</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>], for measuring the insolubility/solubility of HMW

polymers. ECETOC (2013) [ADDIN EN.CITE
<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>] proposed an initial biosolubility screening approach that provided qualitative determinants (*i.e.*, “soluble”, “insoluble”, “Low dissolution rate”, or “Very high dissolution rate”) for assessing biosolubility; however, no quantitative thresholds were provided. In comparison, the International Commission on Radiological Protection (ICRP) and the German Federal Institute for Occupational Safety and Health (FIOSH) provided quantitative biosolubility cutoffs. ICRP describes three categories of soluble radiological materials: Fast (all material rapidly dissolves at a rate of 100 day^{-1}), Moderate (10% of the material dissolves rapidly and the rest dissolves at a rate of 0.005 day^{-1}), and Slow (0.1% of the material dissolves rapidly and the rest dissolves at a rate of 0.0001 day^{-1}) [

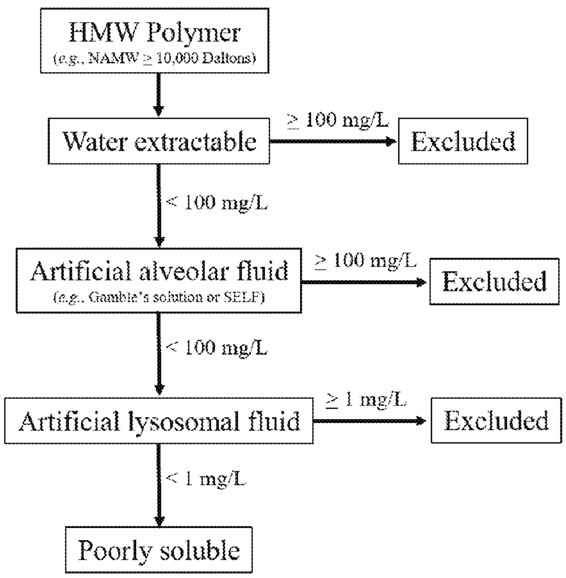
ADDIN EN.CITE

<EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[20]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-

urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. FIOSH proposed a simulated solubility threshold of ≤ 1 mg/L in artificial lung fluids for identifying particles as “low soluble dusts” [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[30]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

As discussed previously, the screening particle size cutoff and percentage of respirable particles for inclusion in this HMW polymer category are ≤ 10 µm and ≥ 1 wt%, respectively. These criteria are readily determinable based on the intended use and life cycle of the HMW polymer. However, determining whether a HMW polymer is “poorly soluble” and a potential hazard concern for lung overload is also dependent on the potential daily exposure estimates. Therefore, we propose using the inclusion/exclusion cutoffs shown in [REF _Ref46673847 \h * MERGEFORMAT], which consider water extractability/biosolubility and the legally binding permissible exposure limit (PEL), as mandated by the U.S. Occupational Safety and Health Administration (OSHA) for respirable particulates not otherwise regulated or PNOR (*i.e.*, 5 mg/m^3).

Scheme [SEQ Scheme * ARABIC]. Screening criteria for determining water extractability and biosolubility.

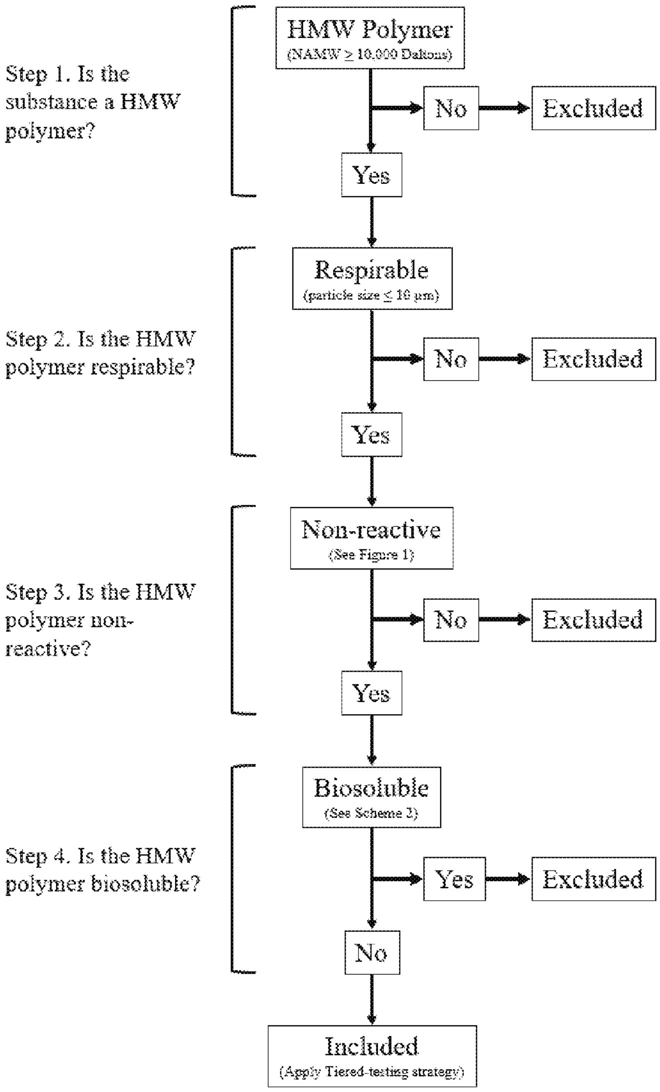


The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first ~~screen~~ step is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility classifications were not specifically established to identify potential hazards related to lung overload and have not been ~~established to correlate~~correlated with biosolubility or biopersistence. Therefore, EPA’s cutoff for moderate water solubility (*i.e.*, 100 mg/L) was selected ~~rather than the low water solubility cutoff~~, since it ~~represents a transition from slight to moderate water solubility and~~ is ~~therefore~~ expected to be conservatively inclusive ~~in the first step because water extractability is generally expected~~and to overestimate the insolubility of polymers in biological fluids. In the second ~~screen~~step, ~~two~~ biosolubility cutoffs ~~may be used,~~are either 100 mg/L or 1 mg/L, depending on the test system used (*e.g.*, simulated epithelial lung fluid or artificial alveolar macrophage lysosomal fluid). These values account for the biosolubility of the HMW polymer, as well as the OSHA PNOR PEL of 5 mg/m^3 (*i.e.*, 50 mg/day; 5 mg/m^3 × 10 m^3/day) for the respirable fraction. The ~~first value is based on EPA (2020)~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>75</RecNum><DisplayText>[31]</DisplayText><record><rec-number>75</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595843741">75</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Revocation of Significant New Use Rule for a Certain Chemical Substance (P-16-581), Proposed rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>18179-18181</pages><volume>85</volume><number>63</number><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]~~, where the Agency applied a~~ biosolubility cutoff of approximately 100 mg/L/day for a polymer in simulated epithelial lung fluid.~~ This value would~~ equates to a mean dissolution rate of approximately 72 mg/day in humans, based on an estimated daily alveolar fluid turnover of 0.72 L [ADDIN EN.CITE

<EndNote><Cite><Author>Fronius</Author><Year>2012</Year><RecNum>58</RecNum><DisplayText>[32]</DisplayText><record><rec-number>58</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595795295">58</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fronius, M.</author><author>Clauss, W.G.</author><author>Althaus, M.</author></authors></contributors><titles><title>Why do we have to move fluid to be able to breath?</title><secondary-title>Frontiers in Physiology</secondary-title></titles><periodical><full-title>Frontiers in Physiology</full-title></periodical><pages>5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357553/pdf/fphys-03-00146.pdf</pages><volume>3</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The second value is based on the German FIOSH biosolubility cutoff of 1 mg/L for granular biopersistent particles. We propose application of this cutoff as a surrogate for estimating the biosolubility HMW polymers in the lysosomes of alveolar macrophages (*e.g.*, artificial lysosomal fluid).

The above screening criteria for respirability, reactivity, and biosolubility provide a framework for determining inclusion/exclusion from the HMW polymer category, as shown in Scheme 2. The screening criteria may be used for determining whether further evaluation of the new chemical substance is warranted using the tiered-testing strategy discussed later in this document.

Scheme [SEQ Scheme * ARABIC]. Framework for determining whether a chemical substance is included/excluded from the HMW polymer category.



Based on the above information, the HMW polymer category was defined to include a variety of respirable, non-reactive (*i.e.*, low toxicity), and poorly soluble HMW (*i.e.*, ≥ 10,000 Daltons) materials, which meet the ~~above-stated~~ criteria for these parameters. HMW polymers ~~meeting these criteria are those which~~ are typically formed through various polymerization processes~~.~~ ~~Chemical substances~~, included ~~are~~ branched and linear polymers, as well as co-polymers produced by random, block, graft, or other techniques. Crosslinked polymers were included in the category because crosslinking can decrease water solubility, but crosslinking was not necessary for inclusion. Therefore, the representative members of this category were refined to include polyacrylates/methacrylates, polyvinyl polymers, polyamides, and polyurethanes/polyureas. The water-dispersible forms polyacrylates/metacrylates and polyurethanes/polyureas would not present hazards for lung overload and are not included in the HMW polymer category [ADDIN EN.CITE ADDIN EN.CITE.DATA]; however, despite their exclusion from the category, they would need to be assessed for other potential hazard concerns. A summary of the structural features of these chemical substances and the chemical boundaries that were established is shown in [REF _Ref46674591 \h * MERGEFORMAT].

[EMBED ChemDraw.Document.6.0]

Figure [SEQ Figure * ARABIC]. Representative members of the HMW polymer category. Structure A, on the left, is representative of polyacrylate/methacylate members, where R is H or methyl; R' and R'' are typically alkyl or substituted alkyl, although there are currently no limits on the substituents. However, charged groups such as carboxyl groups or amine groups would tend to make the polymer dispersible in water rather than insoluble in water. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Acrylamide and methacrylamide monomers (NR'_2 replaces OR' or OR") may also be present. Structure B, on the right, is representative of polyvinyl members, where R is H or C1-C > 20. R' is typically methyl, CN, acetyloxy, Ph or Cl, although there are no current limits on R'. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Copolymers (e.g., including both acrylate/methacrylate and vinyl monomers) are also members of this category. Structure C, on the bottom, is representative of the polyamides group and is made of condensation polymers in which the linkages are all amide functional groups. An example is polycaprolactam, shown.

Hazard Identification

TSCA and its implementing regulations do not require upfront testing on new chemical substances. Therefore, when assessing new chemical substances, EPA generally identifies toxicological analogues to inform the potential hazards for the new chemical substances. The systematic review of the literature was used to identify inhalation studies that assessed endpoints indicative of “overload” for potential toxicological analogues. For the purpose of defining this chemical category, overload has the same definition as identified by EPA (1996) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>59</RecNum><DisplayText>[35]</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797014">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume II of III</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>774, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=219821</pages><volume>EPA/600/P-95/001bF</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]: “This is defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of poorly soluble particles (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in A [alveolar] region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of particles into the interstitium." The relevant studies ~~that were identified~~ are summarized below, followed by the selection of studies on toxicological analogues that may serve as representative points of departure for assessing the potential hazard for overload ~~of some~~for new chemical substances.

Human Data

The hazard concerns discussed ~~herein~~ are limited to chronic effects in the lower respiratory tract of rats exposed to HMW polymers. Epidemiological studies have shown increased lung burdens in workers chronically exposed to poorly soluble particles (PSPs), such as former coal miners; however, studies ~~have shown that~~with rodent models overpredict lung burdens in humans if adjustments are not made for kinetic differences in clearance and retention [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This is consistent with findings from well-conducted epidemiological studies, which have not identified an association between occupational exposure to PSPs and an increased cancer risk. Oberdorster (1995) [ADDIN EN.CITE
<EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[36]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-title></periodical><pages>123-

135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>] concluded that "evidence in humans suggest that particle-overloaded lungs, *e.g.*, in coal workers, respond with fibrosis, but no increased incidence in lung tumors has been found in this group". It has also been reported that "epidemiological data from production workers demonstrate no correlation between PSP exposure and lung cancer or other non-malignant respiratory diseases" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Though these investigations focused on PSPs, the available, yet limited data on HMW polymers provide comparable results. For example, in a recent retrospective study of Xerox workers employed between 1960 and 1982, workers exposed to toner did not show an increased risk of "all-cause" or "cause-specific" mortality. The categories evaluated included cancer (*e.g.*, lung), diabetes, cardiovascular disease, and others [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Aside from this one epidemiological study on toner exposures, the ~~available studies that evaluated~~ evaluation ~~potential hazards from~~of exposures to HMW polymers were limited to inhalation studies conducted in experimental animals as summarized below and described in further detail in Section 2 "Experimental Animal Inhalation Studies on HMW Polymers" of the Supplemental Information file.

Animal Data - Noncancer Effects

Inhalation studies performed in rats and hamsters have demonstrated effects ranging from inflammation to fibrosis after inhalation exposure to several HMW polymers including print toners comprised largely of styrene/butylmethacrylate copolymer and polyvinyl chloride dust. Several of these studies were conducted according to validated test guidelines and under good laboratory practice (GLP) standards, and in some cases published in the peer-reviewed literature. A summary of these studies is provided below.

A series of sub-chronic and chronic studies were performed to test the inhalation effects of a water-insoluble styrene/butylmethacrylate polymer (the primary component of toner used in copy machines) of MW 70,000 in rats. In a subchronic 13-week study, rats were exposed to aerosol concentrations of toner at 0, 1, 4, 16, and 64 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. Dose-related increased lung weight and histological lesions (thickening of alveolar structure due to hypertrophy and hyperplasia of Type II cells) were seen in animals exposed to 16 and 64 mg/m^3. These exposure concentrations also resulted in a dose-related decrease in lung clearance, as measured by the retained quantity of the test substance in excised lungs, and increased lung particle burden [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>]. The NOAEC from this study was 4 mg/m^3.

Bellmann *et al*. (1992) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug

effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>] performed an additional 13-week study using the same test substance ~~used by~~as Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>] and included an extended 15-month post-exposure monitoring period. Rats were exposed to aerosol concentrations of toner at 0, 10, or 40 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study authors measured retention of the toner in the lungs and lung-associated lymph nodes (LALN) by photometric determination in dissolved tissues; clearance was monitored using tracer particles, and pulmonary effects were identified from enzymatic activities and differential cell counts in bronchoalveolar lavage fluid (BALF). The study authors identified clearance half-lives of 277 and 2,845 days for the low- and high-dose exposure groups, respectively, and reported pulmonary effects, as evidenced by increases in protein and enzyme markers of tissue damage in BALF that were partially reversible at 10 mg/m^3 and not reversible at 40 mg/m^3 [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health

Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>].

Muhle *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>] and Bellmann *et al.* (1991)

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[ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1991</Year><RecNum>3</RecNum><

DisplayText>[42]</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844572">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Kilpper, R.</author><author>MacKenzie, J. C.</author><author>Morrow, P.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats</title><secondary-title>Fundam Appl Toxicol</secondary-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>300-13</pages><volume>17</volume><number>2</number><edition>1991/08/01</edition><keywords><keyword>Aerosols</keyword><keyword>Animals</keyword><keyword>Body Burden</keyword><keyword>Dust/adverse effects</keyword><keyword>Female</keyword><keyword>Half-Life</keyword><keyword>Lung/*metabolism</keyword><keyword>Lymph Nodes/metabolism</keyword><keyword>Male</keyword><keyword>Pulmonary Alveoli/metabolism</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Sex Factors</keyword><keyword>Silicon Dioxide/*metabolism</keyword><keyword>Titanium/*metabolism</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590 (Linking)</isbn><accession-num>1662649</accession-

num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1662649</url></related-urls></urls><electronic-resource-num>10.1016/0272-0590(91)90220-x</electronic-resource-num></record></Cite></EndNote>] reported findings from a chronic 24-month exposure study in rats exposed to toner at aerosol concentrations of 0, 1, 4, or 16 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study was performed according to OECD No. 453 Combined Chronic Toxicity/Carcinogenicity Studies ~~and~~ under GLP standards. The study authors reported dose-related impaired particle clearance, elevated lung particle burden, and lung effects (fibrosis, BALF markers of tissue damage, and increased lung weight) at 4 and 16 mg/m^3, with a NOAEC of 1 mg/m^3.

Unpublished subchronic (3 months) and chronic (18 months) hamster studies of the same print toner tested by Muhle *et al.* (1990, 1991) and Bellman *et al.* (1991, 1992) [ADDIN EN.CITE ADDIN EN.CITE.DATA] showed similar effects ~~similar~~ to those in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The unpublished 3-month study was hampered by disease and mortality unrelated to treatment. In the unpublished 18-month study, the hamsters were exposed to concentrations of 0, 1.5, 6, or 24 mg/m^3 for the first 5 months and then concentrations of 0, 4, 16, or 64 mg/m^3 for the remaining ~~time~~test period. At all exposure concentrations, the hamsters exhibited macrophage accumulation, interstitial inflammatory cell infiltration, and bronchiolar/alveolar hyperplasia, along with particle deposits and lymphatic hyperplasia in the LALNs. At the mid- and high-exposure concentrations, fibrosis and alveolar PMN infiltration were noted at the end of exposure and/or after the 5 month post-exposure recovery period; the highest exposure group also exhibited increased lung weight and effects on BALF parameters (increased cell number, macrophage count, LDH, β glucuronidase, total protein, and hydroxyproline). The LOAEC for this study was in the range of 1.5 to 4 mg/m^3.

Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] performed an eight-month inhalation study in rats exposed to an aerosol of PVC powder at 0, 3.3, 8.3, or 20.2 mg/m^3 (MMAD = 1.3 μm; GSD = 2.07; density = 1.3 g/cm^3) for 5 hours/day, 5 days/week. Retention, clearance, and pulmonary effects were evaluated, as reported previously by these same authors. Using radiolabeled (^{85}Sr) polystyrene particles as tracers, these authors showed that pulmonary clearance was significantly decreased in rats after seven months of exposure (25 hours per week) to PVC powder at concentrations $\geq$ 3.3 mg/m^3. Mean alveolar clearance half-times increased with exposure from 1.2-fold higher than controls to 3.2-fold higher than controls at concentrations from 3.3 to 20.2 mg/m^3. The study authors calculated half-times for alveolar clearances of 71, 122, and 184 days at exposure concentrations of 3.3, 8.3, and 20.2 mg/m^3, respectively, supporting that lung overload occurred at concentrations $\geq$ 3.3 mg/m^3 for this water-insoluble polymer.

Animal Data - Cancer

Chronic inhalation exposure data specifically pertaining to HMW polymers are limited to a 24-month rat study of print toner and an 18-month hamster study of print toner [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-

title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>]. No increase~~d~~ in the incidence of tumors ~~incidence~~ was observed in either study; however, interstitial and alveolar lung pathology has been documented in long-term inhalation studies on these polymers. See section on "Animal Data - Noncancer Effects" above.

Supporting Information

An *in vitro* study was identified and reviewed that may be relevant for determining the reactivity/non-reactivity of HMW polymers that do not meet the initial FG and/or FGEW screening criteria.

Wiemann et al. (2016) [ADDIN EN.CITE ADDIN EN.CITE.DATA] developed an *in vitro* assay to test nanoparticles for predicting biologically active ~~toxicity~~ from passive (*i.e.*, overload condition) toxicity. The assay ~~uses~~ used rat NR8383 alveolar macrophages in cell culture medium incubated with test material ~~in cell culture medium, and~~to assesses toxicity *via* measurement of LDH, glucuronidase, and tumor necrosis factor α (TNFα) (after 16 hours exposure), and hydrogen peroxide (after 1.5 hours) ~~in the cell culture supernatant~~. The authors tested 18 inorganic nanomaterials using the assay, as well as corundum as a negative control and quartz DQ12 as a positive control. Based on data from short term inhalation studies, each test material was categorized as either active (NOAEC <10 mg/m^3 for adverse inflammatory action in a 5-day inhalation study) or passive (*i.e.*, inducing nonspecific cell overload). The *in vitro* assay used a particle surface area-based threshold of <6000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL) to determine the biological relevance of the lowest observed significant *in vitro* effects ~~threshold for active toxicity was a surface-area/volume concentration of 6,000 mm²/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL)~~ in at least two of the four measured parameters ~~measured in supernatant~~. The results for the nanomaterials ~~tested~~ showed good ~~correspondence~~ correlation between the *in vitro* and *in vivo* parameters (assay accuracy 95%), suggesting that, the assay could be useful in distinguishing specific ("active") toxicity from nonspecific ("passive" or overload) effects on alveolar macrophages. Although only nanoparticles were tested by these authors, this assay may be useful for screening out HMW polymers for inclusion/exclusion in the category, *e.g.*, those identified as "active" would be inconsistent with the low-concern level and inclusion in the category, whereas those identified as "passive" appear to be consistent with inclusion. Additionally, this assay could be useful for screening polymers with specific toxicities (*i.e.*, excluded from overload category) prior to *in vivo* testing of "overload" for passive polymers.

Quantitative Points of Departure (PODs)

A single epidemiological study of inhaled HMW polymers was identified - the retrospective study of Xerox workers [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This study did not report exposure concentrations associated with the evaluated health outcomes and is therefore not useful for determining quantitative PODs for pulmonary effects of HMW polymers.

A summary of animal studies documenting pulmonary effects after exposure to HMW polymers and the PODs identified from them is provided in [REF _Ref46678612 \h * MERGEFORMAT]. The PODs presented in the table include those from studies meeting the following criteria:

- Exposure was *in vivo via* inhalation (*in vitro*, intratracheal instillation studies were not included);
- Exposure continued for at least 13 weeks; and
- Critical study information was reported, including exposure concentrations, exposure frequency, and aerodynamic particle size (MMAD and GSD).

Each study was evaluated to determine whether the data were amenable for BMD modeling.

~~For the polyacrylates and methacrylates subcategory, s~~Several subchronic studies , for the polyacrylates and methacrylates subcategory that met the initial POD selection criteria, are included in [REF _Ref46678612 \h * MERGEFORMAT] ~~that met the initial POD selection criteria~~; however, BMD modeling was not performed on these studies because chronic studies were available and ~~deemed~~ more relevant for the hazard assessment. Two chronic studies met the

POD selection criteria: the published 24-month rat study of 9000 type toner and the unpublished 18-month hamster study of the same toner [ADDIN EN.CITE ADDIN EN.CITE.DATA]. BMD modeling was performed ~~for the data in~~on the rat study performed by Muhle *et al.* (1991) [ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[41]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords

><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>] ~~, as~~because it used a longer exposure duration, was published in a peer-reviewed journal, and did not change exposure concentrations during the study. ~~, whereas, in t~~The hamster study~~,~~ modified the exposure concentrations ~~were modified~~ after the first five months. ~~Among t~~The endpoints affected at the LOAEC in ~~that~~ the rat study (macrophages, PMN, and lymphocytes in BAL; incidence of pulmonary fibrosis), only the incidence of fibrosis ~~incidence~~ could be modeled, as the BALF parameters were reported without measures of variability (*i.e.*, standard deviation or standard error). The incidences of lung fibrosis (summed across severity categories) were subjected to BMD modeling, as described in Section 3 “Benchmark Dose (BMD) Modeling Outputs” of the Supplemental Information file. The BMCL from the best-fitting model was 2.5 mg/m^3, as shown in [REF _Ref46678612 \h * MERGEFORMAT].

Only a single study was available for the polyvinyl subcategory; however, BMD modeling on the alveolar clearance for the tracer was not possible because of the absence of reported measures of variability ([REF _Ref46678612 \h * MERGEFORMAT]).

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyacrylates and Methacrylates Sub-category							
9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rats, male and female (288/group); 24 months (6 hr/d, 5 d/wk), 2 months recovery	0, 1, 4, or 16	1	4	2.5 (fibrosis)	Significantly decreased macrophages and increased PMN and lymphocytes in BAL; significantly increased incidence of minimal to mild pulmonary fibrosis	[ADDIN EN.CITE ADDIN EN.CITE.DATA]

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
9000 Toner (styrene/butylmet	Syrian Golden Han:AURA Hamster, male and female,	0, 1.5, 6, or 24 (months 1-5); 0,	ND	1.5-4	Not derived; variable	Significantly increased incidences of bronchiolar/alveolar hyperplasia (males); accumulation of particle-laden macrophages in lungs; interstitial	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>30</RecNum><DisplayText>[49]</DisplayText><record><rec-number>30</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849152">30</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner A (styrene/butylmethacrylate random	F344/CrlBR rat, female, (58-66/group); 3 months (6 hr/d, 5 d/wk); up to 6	0, 4, 16, or 64	ND	4	Not derived	Significantly increased incidence slight to moderate accumulation of particle-laden macrophages in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>28</RecNum><DisplayText>[43]</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848985">28</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[40]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author>

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[39]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner B (styrene/ butadiene random copolymer)	F344 rat, female (50 rats/group for main study) up to 6 mo.	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased incidence very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>29</RecNum><DisplayText>[50]</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849070">29</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyvinyls Sub-Category							

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Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

Study Selection for establishing sub-category points of departure (PODs)

In rats, the key events in the development of lung tumors ~~in rats~~ in response to inhalation of inorganic PSPs (as outlined by ECETOC 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>], Bevan *et al*., 2018 [ADDIN EN.CITE ADDIN EN.CITE.DATA], Driscoll and Borm, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Driscoll</Author><Year>2020</Year><RecNum>40</RecNum><DisplayText>[52]</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595775199">40</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Driscoll, K. E.</author><author>Borm, P. J. A.</author></authors></contributors><auth-address>Healthcare Innovation Partners, Princeton, NJ, USA.
Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.
Nanoconsult BV, Meerssen, The Netherlands.
Dusseldorf University, Dusseldorf, Germany.</auth-address><titles><title>Expert workshop on the hazards and risks of poorly soluble low toxicity particles</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>53-62</pages><volume>32</volume><number>2</number><edition>2020/03/10</edition><keywords><keyword>*pslt</keyword><keyword>*hazard</keyword><keyword>*inhalation</keyword><keyword>*lung cancer</keyword><keyword>*lung particle overload</keyword><keyword>*particles</keyword><keyword>*risk</keyword></keywords><dates><year>2020</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0895-8378</isbn><accession-num>32149535</accession-num><urls></urls><electronic-resource-num>10.1080/08958378.2020.1735581</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]) are: (1) impaired pulmonary clearance, (2) persistent neutrophilic inflammation, (3) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and (4) proliferation of cells initiated by secondary genotoxicity (from ROS, RNS, and/or inflammation) and tumor formation.

Though the key events for lung overload from HMW polymers have not been thoroughly studied, the available data ~~as reviewed herein~~ suggests that HMW polymers may lead to lung overload in the rat through similar key events. It should be noted that cytotoxicity to macrophages by a poorly soluble HMW polymer or components present in the polymer may negatively impact clearance *via* alveolar macrophages~~, thereby leading to tumor formation in humans~~. However, substances with these properties (*i.e.*, cytotoxicity) would not be included within the boundaries for the HMW polymers category.

Of the studies listed in [REF _Ref46678612 \h * MERGEFORMAT], PODs of 2.5 mg/m^3 and 3.3 mg/m^3 were identified for the polyacrylates/ methacrylates sub-category and the polyvinyls sub-category, respectively. The 24-month study on the 9000 Toner with a $BMCL_{10}$ of 2.5 mg/m^3 for pulmonary fibrosis was selected as a principle study for polyacrylates/methacrylates because it was the longest duration study ~~on this sub-category of materials~~ and was conducted in the most susceptible species for lung overload (*i.e.*, the rat). Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[46]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] was selected as a principle study for identifying a LOAEC of 3.3 mg/m^3 for the polyvinyls sub-category because it was based on decreased alveolar clearance, which is the first key event in the proposed adverse outcome pathway for lung overload from PSPs in the rat [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These study PODs represent potential starting points for evaluating new chemical substances that fit within one of the HMW polymer sub-categories. EPA may determine that either of these PODs is an acceptable toxicological analogue for chemistries that do not fit within the sub-categories but are anticipated to have ~~comparable or greater~~a potential for ~~causing~~ lung overload in the rat than the new chemical substance under evaluation. For example, EPA generally uses the POD of 3.3 mg/m^3 for quantifying the potential risks of HMW polymers, even for chemistries that would not fall within the polyvinyls sub-category, based on the properties of the new chemical substance ~~compared to the PVC powder~~. Notwithstanding this, we recognize that data on a new chemical substance or an alternative analogue would take precedence over using one of these analogues as the default POD, if EPA concludes there are no study limitations on the new chemical substance or alternative analogue that would preclude the use of those data.

Due to the limited data on HMW polymers, available knowledge about inorganic PSPs was used to make inferences about HMW polymers. Compared to systemic effects, lung overload responses to inorganic PSPs show large variations in susceptibility between and among mammalian species, with the rat being the only species to develop lung tumors [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[29]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. This species-specific response has been explained by species differences in the accumulation of insoluble and respirable particles in the lungs, although cytotoxicity is also an issue with some inorganic PSPs (*e.g.*, crystalline silica). ~~For example, h~~Humans are at least six times more resistant to attaining lung overload conditions than rats for the following reasons: human alveolar macrophages (AMs) are larger (*i.e.*, average volume = 4,990 μm^3) than rat AMs (*i.e.*, average volume = 1,166 μm^3); humans have a greater number of AMs (*i.e.*, average = 7.0×10^9) than rats (*i.e.*, average = 2.6×10^7); and human AMs patrol a smaller surface area (*i.e.*, average = 22,000 μm^2/AM) than rat AMs (*i.e.*, average = 140,000 μm^2/AM) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, the site of retention for poorly soluble particles differs between rats and humans. Nikula *et al*. (2001) [ADDIN EN.CITE

<EndNote><Cite><Author>Nikula</Author><Year>2001</Year><RecNum>62</RecNum><DisplayText>[54]</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803440">62</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nikula, K. J.</author><author>Vallyathan, V.</author><author>Green, F. H.</author><author>Hahn, F. F.</author></authors></contributors><auth-address>Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, USA.</auth-address><titles><title>Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>311-8</pages><volume>109</volume><number>4</number><edition>2001/05/04</edition><keywords><keyword>Adult</keyword><keyword>Air Pollutants/*pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Coal</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Dust</keyword><keyword>Humans</keyword><keyword>*Inhalation Exposure</keyword><keyword>Lung/*chemistry</keyword><keyword>Macrophages, Alveolar</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>*Mining</keyword><keyword>*Occupational